Limin Liao
Helmut Madersbacher
Editors

Neurourology

Theory and Practice

Springer

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ISBN 978-94-017-7507-6 ISBN 978-94-017-7509-0 (eBook)
https://doi.org/10.1007/978-94-017-7509-0

Library of Congress Control Number: 2019930159

This Springer imprint is published by the registered company Springer Nature B.V.
The registered company address is: Van Godewijckstraat 30, 3311 GX Dordrecht, The Netherlands

Foreword

Dear Colleagues,
For some 60 years doctors have been addressing in depth the effects of Neurogenic Bladder Dysfunction on the life expectancy and quality of life of those affected. The decisive factor was not least the desolate and mostly deleterious course of this complication which emerged increasingly through injuries to the spinal cord in the two World Wars. In the following years numerous further illnesses were discovered, the complications of which are similar. The causes are manifold.

Apart from traumatic disorders, inflammatory malignant or hereditary diseases frequently lead to dysfunction of the bladder with the aforementioned consequences.

The therapy for one cause is—as, for example, with paraplegia—seldom or not at all possible for others.

Due to the clinical and scientific efforts of doctors such as Guttmann, Bors and Comarr, Rossier, Scott, Lapides, McGuire, Brindley and others it became possible in the second half of the last century to achieve decisive improvements in the quality of life and life expectancy of these patients.

International scientific societies involved, such as ISCOS, ICS, EAU, AUA—along with many national societies—supported this research with dedication and success.

Also colleagues from the industry's research facilities have contributed important impulses towards the improvement of the clinical situation.

The book/e-book edited by Liao and Madersbacher shows the latest standing of development with all its facets. It represents impressively the current state of development and is a comprehensive complete work of almost all the scientists working in this area.

The current form of an e-book should contribute to spreading the comprehensive contents quickly and globally. I am convinced that it makes extensive information possible for all interested medical specialties.

Our scientific endeavour has led to an enormous wealth of data and therapy options. I would be delighted if these findings lead to an improvement in the quality of life of our patients.

Manfred Stoehrer
University of Essen and TU Munich,
Murnau, Germany

Preface

The reader of this book/e-book may welcome a statement from the editors on the principles underlying the book and a few additional words of explanation. First, the term "neurogenic bladder," includes all disturbances of function and diseases of the bladder due to disorders arising in the central nervous system, peripheral nerves, or intrinsic nerves and ganglia. The term neurogenic bladder is therefore incorrect and misleading. Neurogenic bladder should be replaced by neurogenic lower urinary tract dysfunction, but the term neurogenic bladder is still used worldwide for these diseases.

Neuro-Urology is regarded as a sub-specialty of urology dealing with urinary tract dysfunction caused by acknowledged neurologic diseases or nerve lesions, thus comprising a wide spectrum of different etiologies, pathophysiologies and subsequent functional and secondary structural consequences for the lower and upper urinary tract, then including the diagnosis and treatment for these dysfunctions and complications.

Neuro-urology is a fast-growing sub-specialty. Therefore, an e-book format was chosen, and Springer kindly agreed that the authors could update the chapters every 2 years. Thus, the content of the e-book will more or less parallel developments in the field of neuro-urology.

The aims of this book/e-book are to give an update on neuro-physiology and neuro-pathophysiology of the lower urinary tract, present the principles of the diagnostic evaluation, describe the clinical problems, and inform the reader about the current therapeutic options.

To achieve this purpose, we have invited an impressive number of renowned contributors, including 87 of the most distinguished international experts in this field from 24 countries in Europe, Asia, North America, and South America. The book/e-book is truly an international effort and collaboration. The invited authors are a mixture of older, experienced and younger, very active neuro-urologists. The editors would like to thank all of the authors for their excellent work.

The first part of this book focuses on the basic anatomy of the urinary tract, which will facilitate an understanding of the basic scientific knowledge of innervations and neural control of the lower urinary tract (LUT), clarify the pathophysiologic changes of the upper and lower urinary tracts caused by various nervous system diseases, present the epidemiologic data and risk factors, and describe the classification criteria of neurogenic upper and lower urinary tract dysfunction.

The second part of the book will comprehensively and systematically elaborate the diagnosis and evaluation of neurogenic bladder disorders from the beginning of symptom assessment to the endoscopic examination, focusing on the urodynamic and electrophysiologic examinations of the LUT.

The third part of the book describes the various methods of treatment for neurogenic bladders, including the classic traditional and new controversial methods. With respect to the latter, we have asked the authors to provide evidence-based, objective, scientific, and fair descriptions of the current status, advantages, disadvantages, and future prospects of new therapies.

The fourth part of the book gives a comprehensive account of urinary tract infections, pain, and other complications caused by neurogenic bladders, as well as associated bowel, sexual, and reproductive dysfunction, with an emphasis on the importance of follow-up evaluations.

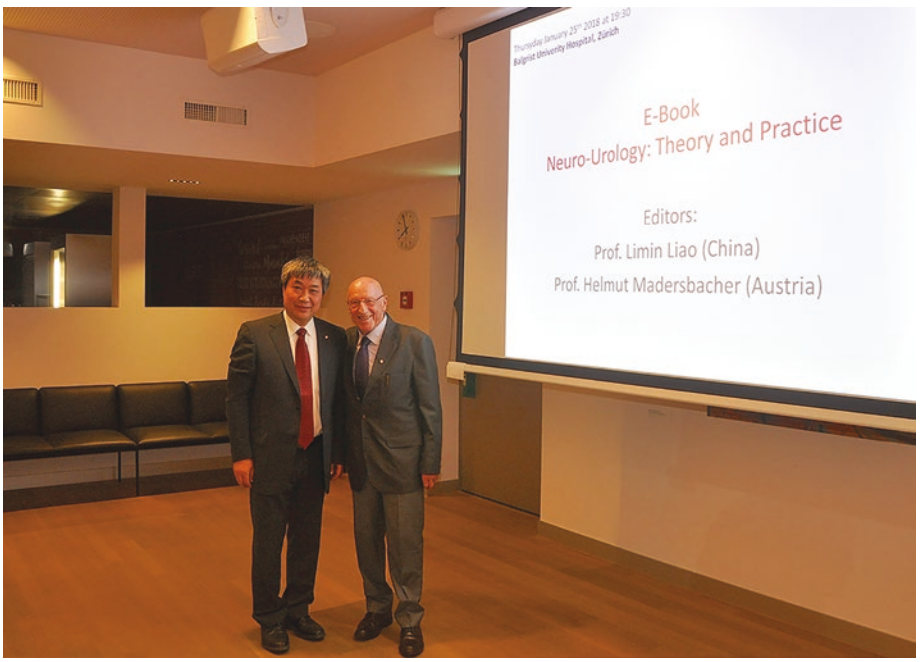
The last part of this book describes the specificity of neurogenic bladders, as caused by ten neurologic diseases, including pediatric neurodevelopmental abnormalities and spinal cord injuries in adults.

Neuro-urology has not yet received sufficient attention, although in the clinical setting we have a large and increasing number of patients with neurogenic bladders who do not receive quality medical care, as well as timely and accurate diagnosis and treatment.

If this book/e-book inspires more medical personnel, especially young colleagues, to develop an interest in neuro-urology, and if it provides senior researchers and clinical practitioners in the field with a valuable cutting-edge reference book, then we will be satisfied as editors.

We are delighted and honored, that Professor Manfred Stöhrer, the former Chief of the Department of Neuro-urology at the Trauma Hospital in Murnau (Bavaria/Germany) and Lecturer on Neuro-urology at the University of Essen, has written the foreword to this book/e-book. Not everybody is aware that it was Manfred Stöhrer who reported for the first time the beneficial effects of botulinum toxin injection into neurogenic overactive bladder at the 1999 International Continence Society (ICS) meeting in Denver.

Finally, we would like to thank Mr. Bing Hu of Springer for his most valuable support of this book/e-book, and the International Neuro-urology Society (INUS) for help during the organization and writing of this book. We also want to thank Drs. Zhao Haitao, Fan Zhang, and Xing Li, as well as Ms. Mag. Irina Anich for help in editing this book. Last, many thanks go to our families for unconditional support.



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E-Book
Neuro-Urology: Theory and Prac
Editors
Prof. Limin Liao (China)

Part I

Anatomical Basis

Anatomy of the Upper and Lower Urinary Tract

1

Erich Brenner

1.1 Introduction

Urine is produced in the two kidneys, conveyed by their respective pelvises and ureters to the bladder where it is stored temporarily, and finally exuded via the unique urethra at the individual's convenience. The kidneys and the ureters form the paired upper urinary tract; the bladder and the urethra build up the unpaired lower urinary tract.

The urethra shows distinct sex differences. Whereas the female urethra is purely urinary, the male urethra serves both urinary and reproductive purposes, of which the latter one is essential, the former merely the use of a tube almost entirely genital.

1.2 Upper Urinary Tract

1.2.1 The Kidneys

The kidneys are composed of structures which passively filtrate the blood plasma forming the primary urine, of structures which actively modify this primary urine by resorption and secretion forming the secondary urine, and several endocrine structures which release erythropoietin, renin, 1,25-dihydroxycholecalciferol and various other soluble factors with metabolic actions.

The kidneys are situated paravertebral in the upper retroperitoneal space, well wrapped up in a specialized adipose tissue. This adipose capsule also embeds the suprarenal glands. In supine position, the cranial border of the upper poles is approximately on the same level with the upper border of the 12th thoracic vertebral body, caudally with the third lumbar vertebra and therefore about 2.5 cm above the iliac crest. The right kidney is usually positioned about 1.5 cm inferior, probably due to the liver's volume on this side. In upright position, the kidneys are situated about 2.5 cm lower; they can ascend and descend slightly with respiration. The left kidney is slightly longer [1, 2] and wider [3] and lies nearer to the median-sagittal plane. Sex differences in renal dimensions are mainly due to the different body height [1]. Renal length decreases with age, and the decrease rate seems to accelerate at 60 years and upward [1, 4].

The long axis of each kidney is orientated infero-laterally, the transverse axis postero-laterally, due to the underlying psoas major muscle.

Each kidney consists of an upper and a lower pole, a convex anterolateral surface, a more or less flat posteromedial surface and a continuously convex lateral border. The medial borders are convex at the poles and concave in between. In this concavity, the renal hilum opens to the renal sinus bounded by anterior and posterior lips. Through the hilum pass the renal vessels, nerves and the renal pelvis, the renal vein usually anteriorly and the renal pelvis posteriorly, with the renal artery in an intermediate position. The renal sinus is lined with the renal capsule and contains the main part of the renal pelvis and vessels. Into the sinus project 4–19 renal papillae (median: 8) resembling the tips of the renal pyramids [5].

1.2.1.1 The Renal Medulla

The renal medulla consists of 4–19 renal pyramids. Each pyramid is cone-shaped with the blunt apex forming the renal papilla. Except for this papilla, the renal cortex surrounds each pyramid forming a renal lobe (renunculus). By fusing several lobes side by side, the cortical tissue in between the pyramids forms the so-called renal columns, which are in fact not columns but partitions or septa ("cloisons de Bertin") [6]. Eight to 130 papillary ducts (of Bellini) open out at each papilla into the minor calices of the renal pelvis [5].

1.2.1.2 The Renal Cortex

The renal cortex embraces each of the renal pyramids except for their papilla. The interpyramidal portions of the cortical tissue are called renal columns. The subcapsular portion of the cortex itself is subdivided into an outer and an (inner)

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_1

juxtamedullary cortex around the bases of the renal pyramids. The arcuate arteries and veins demarcate these two portions. Out of the pyramids' bases medullary rays rise up into the subcapsular cortex.

1.2.1.3 The Renal Parenchyma

The renal parenchyma is composed of a huge number of uriniferous tubules, bound by a little connective tissue comprising blood vessels, lymphatics, and nerves. Each of these uriniferous tubules consists of two embryologically distinct components: the urine-producing nephron and a collecting tubule. These collecting tubules drain several nephrons towards a terminal papillary duct.

The Nephron

The nephron consists of a renal corpuscle, responsible for the initial filtration from the plasma (primary urine), and a renal tubule, concerned with the selective absorption from and secretion into the glomerular filtrate to form the final (or secondary) urine.

There are a half to one million of renal corpuscles per kidney; their number declines significantly with age [7]. They can be found throughout the renal cortex with the exception of a narrow peripheral cortical zone. They have an average diameter of about 200 μm. The (parietal) corpuscular wall (of Bowman) resembles the initial expanded end of the renal tubule and is lined with a squamous epithelium. The visceral sheet engulfing the convoluted glomerular blood vessels is composed of specialized epithelial podocytes. These are flat, stellate cells. Their major processes curve around the glomerular capillaries and interdigitate tightly with each other, forming narrow gaps between these cellular extensions.

The glomerulus is a lobulated collection of convoluted capillary blood vessels covered by the podocytes. Scant connective tissue unites these vascular loops forming a mesangium. The glomerulus is feed by an afferent arteriole which usually enters the corpuscle opposite the exit of the renal tubule; an efferent arteriole emerges at the same site.

The proper renal tubule consists of:

1. a proximal convoluted tubule;
2. a proximal straight tubule entering the medulla;
3. the ansa nephroni (loop of Henle) with
   (a) a thick segment of the descending limb;
   (b) a thin segment of the descending limb;
   (c) the U-turn;
   (d) a thin segment of the ascending limb; and
   (e) a thick segment of the ascending limb.
4. a distal straight tubule;
5. an intermediate macula densa, where the tubule comes close to a glomerulus, and finally;
6. a distal convoluted tubule which finally enters via a junctional tubule into a collecting tubule.

A single layer of mainly isoprismatic epithelium lines the renal tubules, where the type and specific form of the epithelial cells vary according to the functional roles of the different segments.

The mitochondria of proximal convoluted tubule cells are the production site of circulating 1α,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) [8]. The production of $1,25(OH)_2D_3$ at this site is strictly regulated. The parathyroid hormone markedly stimulates $1,25(OH)_2D_3$ production, whereas $1,25(OH)_2D_3$ itself suppresses production.

The collecting tubules hold different cell types, the principal epithelial cells and the intercalated cells [9]. These intercalated cells (IC), also known as mitochondria-rich cells or dark cells, are the "professional" H^+ and HCO_3 transporting cells [10]. The IC exist in two canonical forms: α and β. The α form secretes H^+ into the urine, whereas the β form secretes HCO_3^- into the lumen [10]. Under normal conditions erythropoietin production also occurs mainly in these intercalated cells [11]. In severe hypoxic condition erythropoietin production also takes place in peritubular fibroblastic cells [11].

1.2.1.4 The Juxtaglomerular Apparatus as Site of Renin Production

The afferent and efferent arterioles of a glomerulus enter the mesangium at the vascular pole of a renal corpuscle. In each nephron, the ascending limb of its ansa (loop of Henle) returns from the medulla towards its glomerulus and the intermediate macula densa of the distal tubule and comes in close contact with the afferent and efferent vessels. In this contact area, the cells of the tunica media of the afferent arteriole—and to a lesser extend also the efferent arteriole—differ from smooth muscle cells elsewhere in being large, rounded and granulated with large spherical nuclei and dense vesicles positive for renin. In between the macula densa and the afferent and efferent arterioles lie the so-called Goormaghtigh (G) cells, forming parts of a sensitive nervous body ("corpuscules nerveux sensitifs") [12, 13].

Morphologically and functionally, the afferent arteriole can be divided into a proximal—renin-negative—and a distal—renin-positive—portion. Whereas the media of the proximal portion consists of a monolayer of plain smooth muscle cells not different from those of other resistance vessels, the media of the distal afferent arteriole is composed of renin-producing, granulated cells which are negative for smooth muscle myosin. These cells are often arranged asymmetrically. This distal portion is not limited to the juxtaglomerular region itself but is also found further upstream.

In addition, the efferent arteriole can be divided into a proximal and a distal portion. The proximal portion also comprises renin-positive cells and is not limited to the juxtaglomerular apparatus itself but spreads further downstream.

The G cells show scanty cytoplasm and a chromatin-rich nucleus. They pile up to a cone with the base facing the

macula densa and its apex merging continually into the glomerular mesangium. Human G cells have the shape of a flatly pressed cylinder and are oriented parallel to the basis of the macula densa.

The whole juxtaglomerular apparatus is densely innervated by sympathetic fibers, where single individual axons contact multiple vascular cells and renal tubules [14]. The activation of renal sympathetic nerves leads to volume retention via sodium reabsorption, a reduction in renal blood flow, and activation of the renin-angiotensin-aldosterone system through stimulatory effects on the juxtaglomerular apparatus and subsequent renin release [15]. Additionally to these postganglionic efferent sympathetic fibers, the renal nerves also contain sensory afferent ones [16].

At least two ways of signaling are known, one to the arteriolar smooth muscle cells and another one to the renin producing cells in the glomerular arterioles [17]. Long-term decreases of NaCl intake lead to a reduced NaCl concentration at the macula densa site leading to renin secretion, while increases in the distal delivery of NaCl activate the tubuloglomerular feedback mechanism and contract the afferent arteriole, thereby regulating the single nephron glomerular filtration rate. This latter effect strongly contributes to the autoregulation of the renal blood perfusion and filtration rate.

1.2.1.5 The Renal Vascular System

The complex renal vascular patterns show regional specializations, closely adapted to the spatial organization and functions of the renal corpuscles, tubules, and ducts, and prone to a huge variability.

A single renal artery to each kidney is present in about 70% of individuals, with the others having one to four accessory renal arteries. Whereas the renal artery generally enters the renal sinus via the renal hilum, aberrant renal arteries pierce the fibrous renal capsule outside this hilum; such aberrant renal arteries may arise either directly from the aorta or from the pre-renal branches of the (proper) renal artery. Each renal artery gives off one or more inferior suprarenal arteries and branches which supply the perinephritic tissues, the renal capsule, pelvis, and the proximal part of the ureter. Near to the renal hilum the renal artery splits into an anterior and a posterior division, the primary branches of which (segmental arteries) supply the renal vascular segments. There have been different definitions of arterial segmentation, with the most common distinguishing an apical, a superior, an inferior, a middle, and a posterior segment. Each segment is supplied by a virtual end-artery. In contrast, the larger intrarenal veins have no segmental organization and anastomose freely. The initial branches of the segmental arteries are lobar, usually one to each renal pyramid, but before entering they subdivide into two or three interlobar arteries, extending towards the cortex around each pyramid. At the junction of the cortex and the medulla, interlobar arteries split into arcuate arteries, which diverge at right angles; as they arch between the cortex and the medulla, each divides further, and from their branches, interlobular arteries diverge radially into the cortex. These interlobular arteries ascend towards the superficial cortex or may branch a few times en route. Some traverse the surface as perforating arteries to anastomose with the capsular plexus [18]. Afferent glomerular arterioles are mainly the lateral branches of interlobular arteries. From most glomeruli, efferent glomerular arterioles soon divide to form a dense peritubular capillary plexus around the proximal and distal convoluted tubules. Thus there are two sets of capillaries in series, glomerular and peritubular, linked by efferent glomerular arterioles in the main renal cortical circulation.

From the venous ends of the peritubular capillary plexus fine radicles converge to form interlobular veins, one with each interlobulary artery. Many interlobular veins begin beneath the fibrous renal capsule by the convergence of several stellate veins, draining the most superficial zone of the renal cortex. Proceeding to the corticomedullary junction, interlobular veins also receive some ascending vasa recta and end in arcuate veins which accompany the arcuate arteries, but, in contrast to the arteries, anastomose with neighboring veins. Arcuate veins drain into interlobar veins, which anastomose and converge to form the renal vein.

Efferent arterioles of the glomeruli near the corticomedullary junction provide the vascular supply of the renal medulla, supplemented by some efferent arterioles for more superficial glomeruli, and 'aglomerular' arterioles. These efferent arterioles entering the medulla are relatively long, wide vessels, which, before they enter the medulla, contribute side branches to the neighboring capillary plexus where each of them divides into 12–25 descending vasa recta. These descend to varying depths into the renal medulla, contributing side branches to a radially elongated capillary plexus surrounding the descending and ascending limbs of the renal loops and collecting ducts. The venous outflow converges to the ascending vasa recta which drain into arcuate or interlobular veins. Especially in the outer medulla, the descending and ascending vessels form vascular bundles. As these bundles converge centrally into the renal medulla, they contain fewer vessels, some terminating at successive levels in the neighboring capillary plexus.

Renal lymphatics start with three different plexuses of initial lymphatics: (a) one around the renal tubules; (b) a second one under the fibrous renal capsule; and (c) a third perirenal one within the adipose capsule connecting freely with the second plexus. Within the kidney's parenchyma, lymphatics occur between the tubules of the cortex, accompanying the interlobular and interlobar vessels, but extremely rarely in the medulla [19]. No lymphatics are present in the superficial cortex, the glomeruli and the interstitial tissue between the tubuli [20]. During inflammatory injury, new routes are

created by the de novo formation of lymphatic vessels [21]. Lymphatic collectors from the intrarenal plexus form four or five trunks following the renal vein and end in the lateral aortic nodes. When these trunks leave the renal hilum, the subcapsular collectors join them. The perirenal plexus drains directly into the lateral aortic nodes.

1.2.1.6 The Renal Innervation

The renal plexus is formed by branches from the coeliac ganglion and plexus, the aorticorenal ganglion, the last thoracic and first lumbar splanchnic nerves, and the aortic plexus. Within the renal plexus there are small ganglia; the largest of them is usually situated behind the renal artery's outflow (aortico-renal ganglia) [22].

The lesser thoracic splanchnic nerve, derived from the 9th and 10th or 10th and 11th thoracic paravertebral ganglia, innervates the coeliac and aorticorenal ganglia, which send branches to the renal plexus. The last thoracic splanchnic nerve, derived from the 12th thoracic paravertebral ganglion, synapses directly on the renal plexus. The upper lumbar splanchnic nerve, derived from the first lumbar paravertebral ganglion, sends fibers to the intermesenteric plexus as well as branches that synapse directly on the renal plexus. Fibers from the superior portion of the intermesenteric plexus also run directly to the renal plexus. Additional fibers from the greater splanchnic nerve, the inferior portion of the intermesenteric plexus and the superior portion of the hypogastric plexus may be present in some cases.

As the renal nerves course toward the kidney, the majority of the nerve fibers converges around the renal artery within the adventitia and continues into the kidney around the arterial branches. Contributions from the inferior intermesenteric or superior hypogastric plexus may pass via the gonadal artery and plexus to the superior ureter and inferior aspect of the renal pelvis. There are more nerve fibers on the ventral aspect of the main renal artery than on the dorsal one.

The renal nerves supply the vessels, the juxtaglomerular apparatus, and—mainly—the cortical tubules. They are mostly vasomotoric, but afferent fibers have also been isolated.

1.2.2 The Renal Pelvis

The revulsive urinary system actually starts with the papillary ducts (of Bellini). Nevertheless, the initial isolable part is the renal pelvis within the renal sinus. The renal pelvis consists of the minor and major renal calices and the proper pelvis, which leaves the renal sinus by the renal hilum. Medially to and at the height of the inferior pole of the kidney the renal pelvis proceeds into the ureter.

The minor calices surround the renal papillae. Here, the (internal) renal capsule covering the renal columns in the sinus fuses with the adventitia of the minor calices. A minor calix is trumpet-shaped and surrounds either one or, more rarely, groups of two or three papillae. The minor calices fuse with others, thus forming two or possibly three larger major calices. These major calices fuse again within the renal sinus and thus form the final renal pelvis. Several analyses of the kidney structure showed that the calices and the renal pelvis are extremely variable in shape, ramified (94%) or ampullary (6%), number (3–22, mean 8.15) and location (2–5 groups in case of a ramified shape) [23]. Barcellos Sampaio and Mandarim-de-Lacerda [24] found perpendicular minor calices draining into the surface of the collecting system (11.0%), crossed calices in the mid kidney with the consequent formation of a region that they termed the interpelviocaliceal region (17.1%), calices related to the lateral kidney margin (in 52.9% the anterior and posterior calices were superimposed or alternately distributed), calices related to the polar regions (the superior pole with a midline caliceal infundibulum in 98.6% and the inferior pole with paired calices in 57.9%) and to the mid kidney (with paired calices in 95.7%), and bilateral symmetry of the casts (37.1%).

When the renal pelvis leaves the hilum, it tapers and finally continues into the ureter. Normally, the exact border between the pelvis and the ureter cannot be determined; thus, the term of a 'pelviureteric region' should be used [25].

The wall comprises three distinct histological layers, namely an adventitia being a sheet of connective tissue, a muscular lamina, and an inner mucosal layer. The latter consists of the transitional epithelium (or uroepithelium) and the underlying lamina propria, a sheet of fibro-elastic connective tissue. Although the urothelium appears to be built up by four or five separate layers of cells, all cells reach down to the basal membrane, thus forming a pseudostratified epithelium. The urothelium is composed of three cell types: the cuboidal basal precursor cells, the smaller and spindle-shaped intermediate cells, and the large polyhedral superficial umbrella cells [26]. Each of them may cover one or several cells of the underlying layer. They contain one to two round nuclei, while the cytoplasm presents, at the free surface under the apical plasma membrane, a condensation (the cuticle) that has the function of sealing the mucosa [27]. They are attached to one another near the luminal side by a junctional complex composed of zonulae occludentes, zonulae adherentes and maculae adherentes. These umbrella cells line the lumina of the urinary organs and are responsible for the main specific urothelial functions [26].

Within the muscular wall of the renal pelvis, an autonomous pacemaker system for the pelviureteric peristalsis is located at the border of the minor and major calices [28, 29]. This pacemaker system comprises a specialized type of smooth muscle in the wall of the renal calices and pelvis devoid of non-specific cholinesterase and possessing a number of unusual morphological features. 'Atypical' cells alone

form the muscle coat of each minor calix and extend proximally into the wall of the caliceal fornix. These 'atypical' cells do not form compact bundles; instead, they are separated from one another by connective tissue forming a thin sheet of muscle. However, the inner layer of 'atypical' cells extends only as far as the pelviureteric region, leaving the proximal ureter devoid of a morphologically distinct inner layer [30].

Within the innermost part of the submucosa, nerve fibers (7–8 µm thick) run in longitudinal direction from the calices throughout the pelvis with many transverse interconnections, thus forming a 3-dimensional network or plexus also continuing into the ureter [28].

1.2.3 The Ureter

The ureter is a muscular tube of about 25–30 cm length which conveys urine from the renal pelvis to the urinary bladder by peristaltic contractions. The ureter has a downward inferior and medial trajectory, in the shape of the italic letter "S", both in the transverse and in the sagittal plane [27, 31]. There are three ureteral inflexions: at the level of the inferior pole of the kidney, the marginal flexure (over the pelvic brim) and within the pelvis [27]. The ureter begins in the pelviureteric region; a slight constriction may mark this transition. It descends slightly medially and anteriorly to the psoas major muscle, enters the pelvic cavity by passing over the common iliac vessels, follows the pelvic floor in an anterior direction and finally opens into the base of the urinary bladder. The ureter's diameter is about 3 mm (1.5–6 mm), slightly thinner in the pelviureteric region, the rim of the lesser pelvis near the medial margin of the psoas major muscle, and during its passage through the vesical wall.

Urologists arbitrarily divide the ureter beyond the pelviureteric region into the proximal, middle and distal part whereas in anatomical terminology the course of the ureter comprises three parts: the abdominal, the pelvic and the intramural part. The abdominal part descends retroperitoneally on the medial part of the psoas major muscle, separated from the tips of the lumbar costal processes. The ureter crosses in front of the genitofemoral nerve and is itself crossed by the gonadal vessels. At its origin, the right ureter is overlapped by the descending part of the duodenum. It descends lateral to the inferior vena cava, passes behind the right colic and ileocolic vessels and passes near the pelvic brim behind the caudal part of the mesentery and terminal ileum. The left ureter passes behind the left colic vessels and descends behind the mesosigmoideum in the posterior wall of the intersigmoid recess. The inferior mesenteric artery and its terminal branch, the superior rectal artery, follow a curved course close to the left ureter.

When the ureter passes over the division of the common iliac vessels, either slightly medially over the common iliac vessels (commonly left) or slightly laterally over the external iliac vessels (commonly right), its pelvic part starts. Often underestimated, the pelvic segment of the ureter is approximately 15 cm long and accounts for roughly half of the ureter's total length. At first, it descends posterolaterally in the retroperitoneal tissue (descending part or parietal segment), ventrally to the internal iliac vessels and their visceral branches, along the anterior margin of the greater sciatic notch. Dorsally, marked venous plexuses also accompany it. Projected on to the lateral wall of the pelvis, the descending part of the ureter crosses the obturator artery, vein and nerve. Then, roughly at the level of the ischial spine, the pelvic ureter turns anteromediad into the subperitoneal tissue covering the levator ani muscle and internally towards the base of the bladder (bent part or visceral segment). Progressively it crosses, medially of the umbilical artery, the obturator neurovascular bundle, and the inferior vesical and middle rectal arteries. In males, the bent part of the ureter is crossed anterosuperiorly by the ductus deferens. Then it passes in front and somewhat above the upper pole of the seminal gland and finally enters the bladder wall, accompanied by inferior vesical vessels and the inferior hypogastric (pelvic) plexus. In females, the pelvic ureter initially has the same topographical relations as in males, but anterior to the internal iliac artery, it courses immediately behind the ovary, thus forming the posterior boundary of the ovarian fossa. In its bent part towards the bladder it under-crosses the uterine artery, the uterine cervix, and the vaginal fornices, passing through the broad ligament of the uterus (parametrium), approximately 1.5–2 cm (occasionally even 1–4 cm) away from the margin of the cervix of the uterus. The inferior hypogastric (pelvic) nerve plexus is positioned a little lower than the ureter, with the middle rectal vessels piercing almost at its center. Finally, the terminal female ureter runs forward, accompanied by the neurovascular bundle of the bladder. Just before entering the bladder it passes the anterior vaginal fornix. As a rule, the left ureter has a closer relation to the anterior wall of the vagina than the right one [32].

The intramural segment of the ureter runs obliquely through the bladder wall. Near the bladder, the muscular layer of Waldeyer envelops the terminal ureter. It coalesces with bundles of the detrusor muscle in the bladder wall and consists of coarser longitudinally arranged muscle bundles. Urine reflux is prevented since the ureter passes diagonally through the bladder wall musculature for a short distance before entering the bladder lumen. The length of this intramural part of the ureter in adults is 1.2–2.5 cm (in neonates approximately 3 mm [33]).

At the periureteric region, branches of the renal artery, which supply the renal pelvis, anastomose with the adventitial vascular plexus of the proximal descending part of the ureter (superior ureteral artery). Sometimes, even major descending branches participate in the blood supply of the

upper ureter (30.7%). Branches of the gonadal arteries (middle ureteral artery) supply the following abdominal segment (7.7%). Additional branches derive from the aorta, sometimes forming a proper middle ureteral artery, and the common iliac arteries (15.4%). Overall, the nutrient branches for the abdominal segment of the ureter generally move up from the medial side. By contrast, the descending portion of the pelvic segment of the ureter is supplied by branches of the internal iliac artery (8.5%). These nutrient branches generally move up to the ureter from the lateral side. The bent portion of the pelvic segment of the ureter is supplied by branches of the internal iliac artery, especially the superior vesical artery (inferior ureteral artery) arising from the umbilical artery (12.8%). Moreover, the inferior vesical artery is chiefly engaged in supplying the lower wall of the retrovesical ureter (12.9%). Occasionally, the middle rectal artery also supplies the terminal segment of the ureter. In males, another nutritive branch is the artery to the vas deferens, which can arise directly from the internal iliac or from the umbilical artery. When running together with the vas deferens to the seminal vesicles, it extends branches to the wall of the bent part of the ureter. In females, the uterine artery, additionally supplies the bent portion of the pelvic segment of the ureter as it crosses the ureter. As the crossing is oblique, the ureter is contiguous to the uterine artery for 1–2.5 cm. All these arterial sources present multiple anastomoses, thus forming a periureteral arterial plexus. From this an inner plexus emerges which is characterized by densely convoluted, partly corkscrew-like arteries with small perforating arteries running radially and obliquely upwards and downwards through the intrinsic musculature and continuing to the mucosal vascular plexus.

Venous vessels accompanying the arteries provide the venous drainage towards the inferior vena cava, the iliac veins, and the vesico-genital plexus.

The lymphatic system starts with a network of initial lymphatics in the submucosa, the muscular layer, and the adventitia, and continues with collectors towards the para-aortic, lumbar and iliac lymph nodes. The collecting vessels of the upper ureter mainly join the renal collecting system or pass directly to the lateral aortic nodes near the origin of the gonadal artery; the collecting vessels of the lower abdominal part join the common iliac nodes; the collecting vessels of the pelvic part end in the common, external or internal iliac nodes.

The wall of the ureter comprises an external adventitia, a non-striated muscular layer and an inner mucosa. The ureteric adventitia is assembled by elongated fibrocytes and interwoven bundles of collagenous and elastic fibrils, and is approximately 2.5 mm thick. Numerous blood vessels, lymphatics and nerves intersperse it, mainly orientated parallel to the ureter's long axis. The muscular layer is uniform in thickness and about 750–800 µm in width. In the upper two thirds, a thin superficial circular and a thick deep longitudinal layer can be distinguished. In the inferior third, an additional external layer with longitudinal fibers is added (muscular layer of Waldeyer); it consists of coarser muscle bundles which emerge funnel-shaped from the most external musculature of the bladder wall onto the ureter, separated by a sleeve of connective tissue [27, 34]. The muscle bundles are frequently separated from each other by relatively large amounts of connective tissue. On the other hand, these muscle bundles often form interconnections. Due to the extensive branching, individual muscle bundles do not completely spiral around the ureter [25]. Ureteric muscle bundles consist of closely packed fusiform cells of about 300–400 µm length and 4–7 µm widest diameter. The ureteral mucosa is puckered in longitudinal folds and consists of the transitional epithelium (or urothelium) and the underlying lamina propria, a sheet of irregularly arranged fibro-elastic connective tissue [27]. The latter varies in thickness from 350 to 700 µm. The mucosa contains a vast amount of small blood vessels, many of them accompanied by small non-myelinated nerve fibers.

The ureteric nerves derive from the renal, aortic, and superior and inferior hypogastric plexus. Thus, the ureter is innervated by the lower three thoracic and first lumbar and the second to fourth sacral segments of the spinal cord. The superior hypogastric plexus is a delicate network of sympathetic preganglionic and visceral afferent fibers which are located beneath the level of the peritoneum, just inferior to the bifurcation of the aorta. The hypogastric nerves exit bilaterally at its inferior poles as one to three nerve strands which are the origin of the inferior hypogastric plexus. The pelvic splanchnic nerves (usually arising from the second to fourth sacral segment) traverse the inferior hypogastric plexus before its partition into its specific plexuses for the pelvic viscera. In the female, the branches of the uterovaginal plexus lie a little lower than the uterine artery and the ureter. The branches of the vesical plexus run inferior to the terminal ureter and extend to the trigone of the bladder. In the male, the inferior hypogastric plexus is located 1.5–2 cm dorsal and medial to the vesico-ureteric junction. From its ventrocranial portion the plexus releases the branches to the bladder, the terminal ureter, the seminal vesicle and the vas deferens. The pelvic splanchnic nerves traverse first the dorsocaudal portion of the inferior hypogastric plexus. From there the branches extend to the rectum and the prostate gland as far as the corpus cavernosum of the penis, the so-called erigent nerve(s).

In the adventitia the nerves consist of relatively large axon bundles forming an irregular plexus from which numerous smaller branches penetrate the ureteric muscular layer. These adventitial nerves either accompany the blood vessels or lie free in the adventitia around the ureter, unrelated to the vascular supply. Autonomic ganglion cells can be found only at the extreme lower end of the ureter. Within the ureter, two distinct neuronal networks exist which are in continuity with

the plexus of the renal pelvis. The more prominent plexus sits in the submucosa between the lamina propria and the tunica muscularis, whereas the smaller plexus lies within the smooth muscle fibers of the muscular layer. Both plexuses show frequent interconnections [28]. In the muscularis, the nerve fibers can be found both between and within the non-striated muscle bundles. There is a gradual increase in innervation from the renal pelvis and upper ureter to a maximum in the juxtavesical segment. There are at least three different types of autonomic innervation: a cholinergic, a noradrenergic, and a peptidergic (substance P) innervation. Recently, also a purinergic signaling was described [35]. The intramural plexus consists of unmyelinated visceromotor and viscerosensory fibers.

1.3 Lower Urinary Tract

1.3.1 The Urinary Bladder

The urinary bladder solely serves as reservoir and varies in size, shape, position and relations, according to the volume of the contained urine and the state of the neighboring viscera. When it is empty, it is located entirely in the lesser pelvis but as it distends it expands anterosuperiorly into the abdominal cavity and the preperitoneal space. When empty, it is somewhat tetrahedral and has a fundus, a neck, an apex, a superior and two inferolateral surfaces.

The fundus or base is triangular in shape and oriented posteroinferiorly. In females it is closely related to the anterior vaginal wall, in males to the rectum but its upper section is separated from the rectum by the rectovesical pouch and below that by the vesicular glands (seminal vesicles) and deferent ducts. In a triangular area between the deferent ducts, only the rectovesical fascia separates the rectum and the bladder. The female analogue is the rectovaginal septum [36]; thus the sex-independent common term of a rectogenital septum should be used. The rectogenital septum (known in clinical literature as Denonvilliers' fascia) forms an incomplete partition between the rectum and the urogenital organs in both men and women. Ventrocranially the rectogenital septum constitutes an incomplete partition between the rectum and the urogenital organs, and it is caudally completed by the perineal body [37, 38]. It is composed of collagenous and elastic fibers and smooth muscle cells intermingled with nerve fibers emerging from the autonomic inferior hypogastric plexus [36].

Although the vesical fundus should, by definition, be the lowest part, in fact the neck is lowest and also the most fixed; it is located 3–4 cm behind the lower part of the pubic symphysis. It is pierced by the internal urethral orifice and even with varying conditions of the bladder and rectum it does not alter its position very much. In males, the neck rests on its wall and is in direct continuity with the base of the prostate; in females, it is related to the pelvic fascia which surrounds the upper urethra.

The vesical apex in both sexes faces towards the upper part of the pubic symphysis.

The superior surface, approximately triangular, is covered completely by the peritoneum in males. In females, the superior surface is also largely covered by the peritoneum, but posteriorly this is reflected to the uterus at the level of the internal os of the uterus, thus forming the vesicouterine pouch. The remaining posterior part of the superior surface, devoid of the peritoneum, is separated from the supravaginal cervix by fibroareolar tissue.

The inferolateral surfaces are separated anteriorly from the pubis and puboprostatic ligaments in males or pubovesical ligaments in females, respectively, by a retropubic fat pad and posteriorly by the fasciae of the levator ani and obturatorius internus muscles.

As the bladder fills, it becomes ovoid in shape. It detaches the parietal peritoneum from the suprapubic anterior abdominal wall and slips in-between. In extensive filling, the apex of the bladder may reach the umbilicus or even climb above it. The full bladder's apex points up und forwards above the attachment of the median umbilical ligament; thus, the peritoneum forms a supravesical recess of varying depth between the apex and the anterior abdominal wall.

In both sexes, strong bands of fibromuscular tissue extend from the bladder neck towards the inferior aspect of the pubic bones. These structures are called pubovesical ligaments and constitute the superior extensions of the pubourethral ligaments in females or the puboprostatic ligaments in males. The bilateral pubovesical ligaments lie one on each side of the median plane, leaving a midline hiatus passed through by numerous small veins.

From the apex, the median umbilical ligament, the remnant of the urachus, ascends on the inside of the anterior abdominal wall towards the umbilicus; the covering peritoneum forms the median umbilical fold. The urachus is an embryonic remnant resulting from the involution of the allantoic duct and the ventral cloaca and becomes progressively obliterated during fetal life [39]. The lumen of the lower part of the urachus may persist throughout life and communicate with the bladder cavity [40]. Towards the umbilicus the urachus and the obliterated umbilical arteries blend in a plexus of fibrous bands [41].

The vesical muscosa, attached only loosely to the subjacent musculature for the most part, folds when the bladder empties; as it fills, these folds spread. An exception is the vesical trigone where the mucosa tightly adheres to the subjacent muscular layer and is always smooth.

The internal urethral orifice forms the antero-inferior angle of the trigone, the ureteric orifices its postero-lateral angles. The interureteric crest forms the superior boundary

of the trigone. This crest connects the two ureteric orifices and extends laterally as the ureteric folds, produced by the terminal intramural parts of the ureters. The ureteric musculature contributes directly to the superficial inner layer of the trigonal musculature. Most fascicles run to the midline and blend with those of the opposite side in the interureteric crest. Others spread through the trigone, its lateral margin being formed of somewhat more numerous fascicles directed toward the vesical orifice; yet very few fibers actually descend into the urethra itself [42].

The ureteric orifices are usually slit-like. In an empty bladder, they are about 2.5 cm apart and about the same distance from the internal urethral orifice; when filled, these distances may double.

The internal urethral orifice is usually found in the lowest part of the bladder. In adult males, particularly in those past middle age, immediately behind a slight elevation emerges, caused by the median prostatic lobe, the uvula of the bladder.

The wall of the bladder comprises three distinct layers: an outer adventitial layer, sometimes replaced by a serosal, peritoneal coating, a non-striated muscular layer, commonly known as detrusor muscle, and an inner mucous membrane (mucosa) lining the interior of the bladder.

Relatively thick interlacing bundles of non-striated muscle cells arranged as a complex meshwork construct the detrusor muscle*;* they are electrically coupled by gap-junctions [43]. This meshwork consists of a substantial middle circular layer and both an indistinct outer and inner layer of predominantly longitudinal muscle bundles. The caudal looping of the middle layer ventrally forms the thickest portion of musculature in both sexes. These muscle lamellae eccentrically encircle the internal urethral orifice perpendicular to the longitudinal axis of the urethra. However, the lamellae of the middle circular layer never directly adjoin the internal urethral orifice. The internal urethral or vesical sphincter, which elliptically encloses the internal urethral orifice, is located dorsally, laterally, and ventrally between the orifice itself and the middle layer of the bladder musculature [44].

The internal longitudinal layer is the thinnest of the three layers. The muscle bundles taper from cranial to caudal and end in the form of fibrous tendons at the dorsal circumference of the interureteric muscle [44]. Posteriorly, some of the outer bundles pass over the base of the bladder and fuse with the capsule of the prostate or with the anterior vaginal wall, respectively. Other bundles extend onto the anterior aspect of the rectum (rectovesical muscle). Anteriorly, some of the outer bundles join the pubovesical ligaments, thus contributing to the muscular components of these structures. At the entrance of the ureters into the bladder wall, some bundles of the outer layer extend funnel-shaped onto the outer surface of the ureters (muscular layer of Waldeyer). Similar to the muscular coat of the ureter, an exchange of fibers between adjacent muscle bundles within the bladder wall frequently occurs, thus forming a coherent unit of interlacing smooth muscle.

The smooth musculature of the trigone comprises two distinct layers: a deep outer layer, principally composed of muscles cells of the detrusor muscle and a superficial inner layer consisting of relatively thin muscle bundles continuing from the ureteric musculature (see above). This layer thickens along its superior border to form the interureteric muscle, thus elevating the interureteric crest. Similar, but less prominent, thickenings take place along the lateral margins of the trigone. The overall thickness of the musculature in the trigone increases with age and declines to a low level in the senium; it is higher in males than in females [45].

The ureterovesical junction is quite complex. The ureters pierce the posterior aspect of the bladder and run obliquely through its wall for a distance of 1.5–2.0 cm before terminating at the ureteric orifices. When passing through the detrusor muscle, the ureter is encircled by a sheet of connective tissue, which itself is in continuation with the sheet of connective tissue separating the proper ureteric musculature from the outermost muscular layer of Waldeyer of the terminal or juxtavesical ureter [46]. The mucosa of the ureters continues into the mucosa of the bladder itself, with the anterior-internal portions forming a tender mucosal falciform fold (or valve) over the orifices. The ureteric musculature continues into the superficial inner trigonal musculature, whereas the outer layer of the detrusor muscle encircles the juxtavesical part of the pelvic ureter [47].

The non-striated musculature of the bladder neck is distinct from that which comprises the detrusor proper [48]. In the male bladder neck, the non-striated muscle cells form a complete elliptical collar, which extends distally to surround the pre-prostatic section of the urethra. They form the internal urethral sphincter or vesical sphincter [44]. Distally, the bladder neck musculature merges with the stroma and capsule of the prostate gland. The female bladder neck seems generally more thickset due to the clearly shorter urethra compared to the male. This is also reflected in the course of the vesical sphincter. The muscle bundles embrace the bladder outlet in a more circular, less elliptical fashion. They are located around the proximal third of the urethra and are directly adjacent to the external urethral sphincter. As a whole, the vesical sphincter is clearly less distinctive in women than in men, however, it corresponds in all age groups to those in the male [44]. As in males, the female internal urethral sphincter does not originate from the bladder detrusor [49].

Throughout the detrusor muscle, c-kit-immunoreactive interstitial cells can be found. These cells are located at the junctional area between the inner circular and outer longitudinal smooth muscle fibers. They display the morphologic characteristics of cells that were formerly defined as the

interstitial cells of Cajal or pacemaker cells in the gastrointestinal tract. In the superior vesical wall, an accumulation of such c-kit-immunoreactive interstitial cells was identified. It consists of small groups of accumulated cells surrounded by layers of connective tissue cells and fibers [50].

The mucosa of the bladder has a structure similar to that of the ureters and consists of a transitional epithelium, supported by a layer of loose connective tissue. This lamina propria consists of loose fibro-elastic connective tissue and forms a relatively thick layer, varying in thickness from 500 μm in the fundus and inferolateral walls to about 100 μm in the trigone. Small bundles of non-striated muscle cells occur in this submucosa, forming an incomplete and rudimentary muscularis mucosae. The connective tissue elements immediately below the transitional epithelium, particularly in the trigonal region, are densely packed. At deeper levels, they are more loosely arranged. Thereby the bladder mucosa is able to form numerous thick folds when the volume contained within the lumen is small. Throughout the submucosa an extensive network of blood vessels is present and supplies a plexus of thin-walled fenestrated capillaries lying in the grooves at the base of the urothelium. Besides this plexus, the lamina propria contains several types of cells, including fibroblasts, adipocytes, interstitial cells, and afferent and efferent nerve endings [51].

Outside the trigone, the urethelium comprises up to six cell layers; one layer of umbrella cells, one or more layers of smaller intermediate cells, and one layer of undifferentiated basal cells. Within the trigone the urothelium is flat and usually consists of only two or three cell layers. Additionally, in the neck and trigone a fourth cell type occurs. This consists of flask-shaped cells which extend throughout the whole depth of the urothelium. Numerous large membrane-bound vesicles, each containing a central dense granule, characterize them.

The identification of functional receptors/ion channels in the urothelial cells of the bladder and the involvement of these sensor molecules in the release of chemical mediators (nitric oxide, NO; ATP) suggest that urothelial cells exhibit specialized sensory and signaling properties. Such mechanisms might allow them to respond to their chemical and physical environments and to engage in reciprocal communication with neighboring urothelial cells as well as nerves in the bladder wall [52].

The principal arteries supplying the bladder are the superior and inferior vesical arteries. The superior vesical artery is the major and final branch of the patent rest of the umbilical artery, which originates from the anterior trunk of the internal iliac artery. The inferior vesical artery originates directly from the internal iliac artery, often together with the middle rectal artery, and supplies the vesical fundus, prostate, seminal gland, and the lower ureter. The inferior vesical artery sometimes provides the artery to the ductus deferens. Two major vascular plexuses (adventitial/serosal and mucosal) and two distinct capillary networks (muscular and subepithelial) can be distinguished in the successive layers of the wall. Almost all bladder vessels except the capillaries show an extensive tortuosity ranging from waviness to tight coiling. Larger branches of the main extravesical arteries and veins form the adventitial/serosal plexus characterized by a highly tortuous course of the vessels and numerous anastomoses. This plexus supplies and drains the capillary network of the detrusor muscle and sends long, perpendicular vessels piercing the detrusor muscle itself and communicating directly with the mucosal plexus. The perpendicular vessels are almost straight, wavy, tortuous, or tightly coiled, depending on whether they join the mucosal plexus near the top or near the base of the respective mucosal fold. The mucosal plexus consists of some capillaries, thin arteries and more numerous, thicker veins, presenting a tortuous appearance and frequent interlacements; it forms a distinct vascular layer parallel to the inner surface of the bladder, following the profiles of the mucosal folds. Short non-anastomosing arteriolar and venular twigs, often perpendicular to the surface plane and sometimes forming a palisade-like pattern, leave the upper aspect of the plexus and communicate with the subepithelial capillary network. The subepithelial capillaries form an extremely dense, planar meshwork. Only in the trigonal area and around the urethral orifice are they arranged in the form of a looser network with elongated meshes. The detrusor muscle itself contains occasional, very tortuous arterial and venous branches mostly derived from the adventitial/serosal plexus, and a poorly developed, irregular capillary network consisting of thin, uniform vessels. The vessels of the detrusor muscle are distributed in flat sheets probably corresponding to the connective tissue septa between the smooth muscle bundles [53].

The initial lymphatics start in the mucosal, intramuscular and extramuscular plexus. In the subepithelial layer lymphatics are rare. Within the deeper submucosa lymphatics are consistently present. They are often adjacent to and intermingled with arterioles and venules [54]. Lymphatic vessels, although small, are predominantly distributed in the detrusor muscle compared with the other layers; the tightest plexuses are situated at the borders between the submucosa and the detrusor as well as the detrusor and the adventitia [55]. Almost all collecting vessels end in the external iliac nodes. There are three sets: lymphatics from the trigone emerge on the vesical exterior to run superolaterally; those from the superior surface converge to the posterolateral angle and pass superolaterally across the lateral umbilical ligament towards the external iliac nodes; those from the inferolateral surface ascend to join those from the superior surface.

The nerves supplying the bladder form the vesical plexus and contain both efferent and afferent fibers. This vesical plexus from the anterior part of the inferior hypogastric

plexus comprises many filaments which pass along the vesical arteries to the bladder. Branches also supply the seminal glands and deferent ducts. In addition to the branches from the vesical plexus, small groups of autonomic neurons occur throughout all regions of the bladder wall. Numerous preganglionic autonomic fibers form both axosomatic and axodendritic synapses with these ganglion cells. The bladder, including the trigone, is profusely supplied with nerves forming a dense plexus among the detrusor smooth muscle cells. Terminal regions approach to within 20 nm of the surface of the muscle cells and are either partially surrounded by or more often totally denuded of Schwann cell cytoplasm. The lamina propria of the fundus and inferolateral walls is virtually devoid of autonomic nerve fibers, whereas at the bladder neck and the trigone a nerve plexus extends throughout the lamina propria.

1.3.2 The Female Urethra

The female urethra is about 4 cm in length and 6 mm in diameter. It starts at the internal urethral orifice of the bladder and runs antero-inferiorly behind the pubic symphysis, embedded in the anterior wall of the vagina. It traverses the urogenital diaphragm and ends at the external urethral orifice, an antero-posterior slit with rather prominent margins. This orifice lies directly anterior to the opening of the vagina and about 2.5 cm behind the glans clitoridis. Except for the passage of urine, the lumen forms a transverse slit with the anterior and posterior wall in apposition. Many small mucous urethral glands and small lacunae open into the female urethra. Near the lower end, a couple of these glands are grouped together on each side and open into the para-urethral duct; each duct descends in the submucosal tissue and ends in a small aperture on the lateral margin of the external urethral orifice.

Throughout its pelvic course the female urethra has no direct ligamentous fixation to the pubic bone. Ventrolaterally, the urethra is enclosed by the ventral parts of the levator ani, its fasciae, and a ventral urethral connective tissue bridge connecting both sides. Dorsally, the urethra is intimately connected to the wall of the vagina [56].

The muscular wall of the female urethra consists of an outer sleeve of striated muscle, the external urethral sphincter, together with an inner layer of non-striated muscle fibers. The constituent fibers of this external urethral sphincter are circularly arranged and form a sleeve which is thickest in the middle first third of the urethra. The female external urethral sphincter system includes a true annular sphincter around the urethra (urethral sphincter, a part that passes anterior to the urethra and attaches to the ischial rami (compressor urethral muscle), and a part that encircles both the urethra and the vagina (urethrovaginal sphincter) [57].

As in males, the muscle fibers are quite thin and of the slow twitch type. The inner smooth muscle layer extends throughout the length of the female urethra and consists of thin muscle bundles which are orientated obliquely or longitudinally.

The mucous membrane is continuous with that of the bladder. It consists of a stratified transitional epithelium and a supporting layer of loose fibro-elastic connective tissue (lamina propria). This lamina propria contains an abundance of elastic fibers, which are arranged either longitudinally or circularly around the urethra, as well as numerous thin-walled veins. Proximally the female urethra is lined by the characteristic urothelium; nevertheless, distally the epithelium changes into a non-keratinized stratified epithelium lining the major portion of the female urethra. At the external urethral orifice this epithelium keratinizes and becomes continuous with the skin of the vestibule.

The constitution of the glands surrounding the human female urethra has been under debate; especially regarding as to what extent they equal the male prostate; a female prostate was found in a majority of women and can be distinguished from other urethral caverns and immature paraurethral ducts. Their glands consist of tubulo-alveolar acini at the end of one excretory duct, leading to the urethral lumen and are distributed mainly laterally or dorsolaterally of the urethral axis [58, 59].

A large number of unmyelinated nerve fibers are scattered throughout the connective tissue at the level of the proximal urethra. These nerve fibers are distributed in the smooth muscle layers of the vagina and urethra. Although these autonomic nerve fibers are predominantly located at 4 o'clock and 8 o'clock, they tend to spread throughout the periurethral connective tissue. Several myelinated nerve fibers accompany the unmyelinated fibers in the space between the anterior vaginal wall and the posterior surface of the urethra. At the level of the sphincter and distal urethra unmyelinated nerve fibers travel along the lateral vaginal walls and on the posterior surface of the urethra. These fibers penetrate the smooth muscle layers through the lateral walls and spread in the submucosa, smooth muscle layer and the transitional zone between the external smooth and the internal striated circular fibers [60].

Lymphatics from the complete female urethra pass mainly to the internal iliac nodes; a few may end in the external iliac nodes. Lymphatics from the membranous urethra accompany the internal pudendal artery.

1.3.3 The Male Urethra

The male urethra extends from an internal orifice in the urinary bladder to an external orifice, or meatus, at the end of the penis. Four distinct sections can be described:

a pre-prostatic, a prostatic, a membranous, and a spongiose section. When the penis is in its usual flaccid state, these sections form a double curve. Except during the passage of fluid, the urethral canal is a mere slit. In the prostatic section, this slit is transversely arched, in the membranous section it is stellate, in the spongiose section again transverse, while at the external orifice it is sagittal in orientation.

The pre-prostatic section of the male urethra has a stellate lumen. It is about 1–1.5 cm long, extending almost longitudinally from the bladder neck to the superior aspect of the prostate gland. The non-striated musculature surrounding the pre-prostatic urethra forms a distinct elliptical collar which distally becomes continuous with the capsule of the prostate gland. The bundles forming this internal urethral sphincter (or vesical sphincter) are separated by connective tissue containing many elastic fibers.

The prostatic section of the male urethra is approximately 3–4 cm long and, behind the fibromuscular stroma of the isthmus tunnels, through the prostate. Throughout most of its length the posterior urethral wall shows a midline ridge, the urethral crest, which projects into the lumen causing it to appear crescent in transverse section. On each side of the crest there is a shallow depression, the prostatic sinus, into which enter the orifices of the prostatic ducts. About the middle of the length of the urethral crest the colliculus seminalis (or verumontanum) forms an elevation on which the slit-like orifice of the prostatic utricle is situated. On both sides of or just within this orifice enter the ejaculatory ducts. Distally the prostatic urethra possesses an outer layer of circularly disposed striated muscle cells which are continuous with a prominent collar of striated musculature, the external urethral sphincter, within the wall of the membranous urethra. The urethra leaves the prostate slightly anterior to its apex, the most inferior point.

The membranous section is the shortest, least dilatable and, with the exception of the external orifice, the narrowest section. It descends with a slight ventral concavity from the prostate gland to the bulb of the penis, passing through the urogenital diaphragm about 2.5 cm postero-inferior to the pubic symphysis. The posterior part of the bulb is closely apposed to the inferior aspect of the urogenital diaphragm but anteriorly it is slightly separated from it, so that anteriorly the wall of the urethra is related neither to the urogenital diaphragm nor the penile bulb. This part of the anterior wall of the urethra is regarded as the 'membranous' part; anteriorly it is about 2 cm long, whilst posteriorly it is only 1.2 cm. The wall of the membranous urethra consists of a muscle coat which is separated from the urothelial lining by a narrow layer of fibroelastic connective tissue. This muscular coat consists of a relatively thin layer of non-striated muscle bundles continuous proximally with those of the prostatic urethra, and a prominent outer layer of circularly orientated, usually quite thin striated muscle fibers forming the external urethral sphincter. This external urethral sphincter, composed of slow twitch fibers, is devoid of muscle spindles and supplied by the pelvic splanchnic nerves.

The spongiose section is embedded in the corpus spongiosum penis. It is about 15 cm long. Commencing below the urogenital diaphragm, it continues the ventrally concave curve of the membranous urethra to a point anterior to the lowest level of the pubic symphysis. From there the urethra curves downwards in the 'free' part of the penis, when it is flaccid. The spongiose section is quite narrow (6 mm in diameter), and is dilated at its beginning forming the intrabulbar fossa and again within the glans penis forming the navicular fossa (up to 8–9 mm in diameter). The bulbourethral glands (Cowper) open into the spongiose section about 2.5 cm below the urogenital diaphragm; their orifices are 2–3 mm apart. The external orifice is the narrowest part of the urethra: it is a sagittal slit, about 6 mm long and bounded on each side by a small labium.

Except for the most anterior part within the glans penis, the epithelium of the urethra exhibits the orifices of numerous small mucous glands and follicles situated in the submucous tissue (urethral glands). Additionally, there are three to eleven small pit-like lacunae of varying sizes; the largest of them, the lacuna magna, is situated at the roof of the navicular fossa. The epithelial lining of the pre-prostatic and proximal prostatic urethra is of urethelial type as in the bladder. Below the openings of the ejaculatory ducts the epithelium changes to a patchily pseudostratified or stratified columnar variety which lines the membranous urethra and the major portion of the spongiose urethra. Mucus-secreting cells are common throughout this epithelium and frequently form small clusters in the spongiose urethra. Here the mucous membrane shows many recesses which continue into deeper branching tubular mucous glands (of Littré) which are especially numerous on the dorsal aspect. Within the proximal navicular fossa, the epithelial lining changes, sharply demarcated, to a non-keratinized, stratified squamous epithelium with well-defined connective tissue papillae. At the external urethral orifice, the epithelium keratinizes.

At the level of the bladder neck nerve fibers run under the pelvic fascia on either side of the rectovesical pouch, lateral and cranial to the rectum and the seminal vesicles, and penetrate into the bladder neck at 5 o'clock and at 7 o'clock. The autonomic nerves run beneath the fascia of the levator ani muscle along the posterolateral surface of the rectum, around the anterolateral aspects of the seminal vesicles and over the inferolateral aspect of the prostate. At this level nervous myelinated and unmyelinated fibers can be found on the posterior face of the bladder neck. Some unmyelinated fibers follow the ejaculatory ducts of the cranial prostate to reach the prostate and the prostatic urethra. At the level of the prostate and of the prostatic apex unmyelinated nerve fibers are situated outside and behind the prostatic capsule.

They send numerous branches following the ejaculatory ducts through the prostate gland until they reach the urethra at the level of the seminal colliculus. These branches also innervate the smooth muscular fibers of the prostatic urethra and the submucosa. At the level of the membranous urethra most of the autonomic nerve fibers penetrate the urethral sphincter muscle from the posterolateral surface and most of the myelinated nerves enter the urethral sphincter from the anterolateral surface [61].

Lymphatics from the prostatic and membranous urethra pass mainly to the internal iliac nodes; as in females, a few may end in the external iliac nodes. Lymphatics from the spongiose urethra accompany those of the glans penis, ending in the deep inguinal nodes. Some of them end up in medial superficial nodes; others traverse the inguinal canal and end in the external iliac nodes.

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Part II

The Innervation and Neural Control of the Lower Urinary Tract

Sensor and Transducer Function of the Urothelium

2

Changhao Wu

The urothelium, the epithelial layer of bladder mucosa, has the classic barrier function of preventing harmful urinary constituents from leaking into the underlying submucosal structures and smooth muscle. In recent years, this epithelial layer has been recognised as a new sensory structure that responds to bladder distension as well as pathological stimuli. This has changed our view on bladder sensory mechanisms and generated intense interest in its role in pathophysiology underlying many bladder disorders.

2.1 Urothelium as a Sensory Structure

2.1.1 Urothelium and Barrier Function

The urothelium is a transitional epithelium with morphology lying between the pseudo-stratified epithelium and truly stratified epithelium [1]. There are essentially three layers of cells in this epithelium: a basal layer of small cells (5–10 μm in cell diameter), a middle/intermediate layer of pear-shaped cells of different size and height (20 μm in cell diameter), and a layer of surface cells (umbrella cells) of large size (50–150 μm in cell diameter) with multiple nuclei. Although the urothelium has a slow turnover under normal conditions (turnover rate of approximately 200 days) [2], progenitor cells are found throughout the urothelium. The basal layer contains stem cells which divide and fuse to form the intermediate cells, and cells from this intermediate layer in turn fuse to form the umbrella cells.

The urothelium has two basic physiological characteristics: the ability to accommodate the stretch and a high transepithelial electrical resistance [2].

During distension, the stretched bladder epithelium is thinned and retains the essentially three-layer appearance. The surface cells become flattened and thus the surface area increased. When the bladder is in the collapsed state, the mucosa is highly folded and the urothelium appears to have 6–7 layers.

The bladder urothelium serves as an effective physical barrier with low permeability to water, urea, ammonia and H^+ ions [3–7]. The permeability barrier function is mainly provided by the apical umbrella cells. Most of the apical surface area is covered by polygonal-shaped protein plaques composed of uroplakins. Surface umbrella cells are joined by the tight junctions. These tight junctions are composed of 5–6 bands of interconnecting strands. The movement of urine solutes across the urothelium can take place through either a trans-cellular (through the cells) or para-cellular (through the tight junction and the lateral intercellular space, in the three cell layers) route. Impedance and freeze fracturing EM data show that intermediate and basal cell layers do not offer significant barrier to the movement of the substances between urine and blood and the apical cells are not well coupled to the lower cell layers by gap junctions [8, 9]. Therefore, the major barrier to the movement of solutes from urine to blood is the combination of the surface umbrella cells and the tight junction. Both pathways exhibit very low permeability to electrolytes and non-electrolytes.

2.1.2 Alterations to Urothelial Barrier Function

The tight barrier of the bladder epithelium can be damaged by pathological factors. These noxious stimuli can be biological (bacterial infection, inflammation), chemical (drugs and toxic substances, pH) and physical (radiation) factors. Examples are bacterial cystitis and interstitial cystitis (biological), cyclophosphamide-induced haemorrhagic cystitis (chemical), and irradiation-induced cystitis (physical). The causes and mechanisms for the loss of barrier function are multifaceted. The common mechanisms include loss of tight junctions, loss of surface cells, and alteration in apical membrane structure [10].

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_2

Specific mechanisms and signalling pathways are also involved in different conditions. For example, in interstitial cystitis, a syndrome characterised by severe bladder pain, the epithelial integrity can be damaged during the inflammatory process. Disruption to epithelial integrity in this condition may be due to release of some substances such as antiproliferative factor, which inhibit the proliferation of bladder urothelial cells and affects the barrier function [11, 12]. Changes to the release of these mediators from the urothelium can not only affect the integrity of the epithelium but also the intercellular communications. Injury, inflammation or cystitis increase the levels of endogenously generated mediators such as NO [13] which cause an increase of permeability to water and urea in addition to ultrastructural changes in the apical urothelium [10, 14]. Injury and inflammation may also increase the release of stress hormones [15], and stress has been shown to cause a breakdown of the blood-urine barrier by inducing local detachment of tight junctions followed by dysfunction of adherens-type junctions and consequent detachment and desquamation of urothelial cells [16]. Apoptosis may also be involved in the loss of urothelial cells in interstitial cystitis [17]. Infectious cystitis, on the other hand, causes extensive dysfunction of the blood urine barrier and localised mechanical disconnection of adhesive junctions which consequently leads to desquamation [14]. Spinal cord transection alters the urothelial barrier function probably due to increased sympathetic outflow or increased circulating catecholamines, and capsaicin-sensitive afferents may play a protective role in the process [18].

As a result of the loss of barrier function, trans-epithelial resistance is decreased and permeability to urinary constituents is increased, hence their movement from the apical surface to the baso-lateral surface and detrimental pathological consequences. For example, in non-infectious cystitis, leakage of urinary constituents through the damaged epithelium may exacerbate the inflammation in the underlying muscle layers. In view of the new concept of the sensory function of the urothelium as discussed later, damaged barrier function has important implications in the sensory disorders of the bladder (see Sect. 3).

2.1.3 Urothelium as a New Sensory Structure

The concept that the bladder urothelium functions as a sensory structure to detect the fullness of the bladder was first proposed by Ferguson [19] following the seminal experiment which showed that distension of the bladder wall caused the release of ATP from the bladder mucosa and ATP was suggested as a sensory mediator for distension and other sensory cues. Rong et al. later provided the direct evidence that ATP analogues were able to stimulate the firing of the bladder afferent fibres [20]. The sensory transduction of the bladder urothelium was substantiated by the evidence for the expression of purinergic receptors on the sensory nerves to receive the chemical signal of ATP, in particular P2X receptors [21]. The physiological relevance of P2X sensory signalling was demonstrated from the experiments which showed that molecular deletion of P2X3 receptor suppressed bladder afferent nerve activity and also the micturition reflex, and caused urinary retention [21, 22]. Indeed, afferent nerves that contain peptides terminate within the lamina propria (the suburothelium) and within the transitional epithelium itself. Classically these sensory nerves in the lamina propria are C-fibres and contain CGRP and substance P [23, 24]. More recent study reveals that these sensory nerve endings may also express P2X3 receptors [21]. Whether all of the CGRP and substance P positive sensory nerves express P2X receptors has yet to be determined.

In addition to P2X receptors, vanilloid receptors are also found on the sensory nerves [25]. TRPV1 deletion also leads to attenuated micturition reflex [26]. Thus these data suggest that these sensory fibres not only respond to noxious stimuli but also respond to distension—the physiological stimulus for the bladder.

2.1.4 Urothelium and Suburothelial Interstitial Cell Network as a Functional Syncytium

Another significant advance was the demonstration of a dense network of suburothelial interstitial cells—myofibroblasts, identified by their labelling to c-kit and vimentin, as well as their morphology [27–29]. Interstitial cells are found throughout the bladder wall: in the suburothelium; around and within muscle bundles; and at the serosal surface [30–32]. They are not a homogenous group of cells as their responses to agonists such as carbachol vary [33, 34], and their electrophysiological properties are different [35–37]. Importantly myofibroblasts labelled strongly for the gap junction protein connexin-43, located to gap junctions between adjacent cells [32], and associate intimately with sub-urothelial nerves [27, 38]. Myofibroblasts also express NO synthase and NO-induced cGMP-immunoreactivity, as with other interstitial cells [31, 39, 40], and are targets of efferent nitregic nerves [31, 41]. This suggests that their activity in turn may be neurally modulated generating a potentially complex control system. Thus their location, network-like distribution, presence of Cx43-containing gap junctions, and close contact with sensory and efferent nerve endings lead to the proposal that suburothelial myofibroblast network has the role of linking the urothelium to afferent nerves with the gain of function.

For myofibroblasts to be a functional interface, a prerequisite is that they respond to ATP and noxious stimuli. Experiments show that myofibroblast cells respond to ATP and other nucleotides with transient rises of intracellular [Ca^{2+}] and then depolarization by a Ca^{2+}-dependent Cl^- current: immunostaining identified a $P2Y_6$ receptor [34, 35, 42]. Vanilloid receptors are also located on myofibroblasts [43], so they could also mediate noxious stimuli such as acidosis [44].

2.2 Physiological Properties of the Urothelium and Polymodal Sensing

Recent experiments show that the urothelium has distinct physiological properties and receptor profiles and also has intricate interactions with other neuronal and non-neuronal cell types in the sub-urothelial space. These features allow the urothelial associated tissue compartment to receive a wide range of input of sensory cues and perform polymodal sensing.

2.2.1 Physiological Properties of the Urothelium

A large variety of receptors have been shown to exist in the urothelial cells. Fewer functional studies on these receptors have been carried out in urothelial cells, especially in the native urothelial cells. The native urothelial cells show spontaneous Ca^{2+} activations and also respond to hypotonic stretch probably mediated by stretch activated channels [45]. ATP and its analogues cause a rise of intracellular Ca^{2+}, demonstrating that purinergic receptors are the functional receptors. With urothelial sheets the transepithelial potential (TEP) can be influenced by ATP or Na^+ gradient. This suggests that urothelial cells can respond to ATP - an autocrine effect which would amplify the effect of ATP released from themselves. The functional purinergic receptors on the urothelial cells are P2Y receptors, distinct from P2X receptors in the detrusor smooth muscle cells. A further distinction of the urothelial cells from the smooth muscle cells is the lack of Ca^{2+} response to muscarinic agonists which typically cause significant Ca^{2+} rise in detrusor smooth muscle cells. Furthermore, urothelial cells are epithelial cells in nature and would not be able fire action potentials. There is no evidence for the existence of typical fast Na^+ channels and Ca^{2+} channels in urothelial cells.

2.2.2 Expression of Multiple Receptors on the Urothelium to Receive Sensory Inputs

Most muscarinic receptor subtypes are located on the urothelium which may modulate urothelial sensory activation. Many other sensory receptors, typically expressed in primary afferents, are also present on urothelial cells. These include receptors to nicotine, P2 receptor agonists (P2X and P2Y) [46, 47], $TRPV_{1,2,4}$ [26] $TRPA_1$ [48], $TRPM_8$ [49], adrenergic agents [50], bradykinin (B1, B2) [51], prostaglandin E (subtype EP_1) [52], adenosines (A1, A2a, b and A3) [53], estrogen receptors (Erα, Erβ) [54], mechanosensitive epithelial sodium channels (ENaC) [55], and nerve growth factor [56].

Thus there is an extensive collection of nociceptive and mechanoreceptive receptors and ion channels in the urothelium. These "sensor molecules" enable the urothelium to respond to a range of sensory inputs such as increased stretch during bladder filling (mechanical), soluble factors in the urine (purines and nerve growth factor) and chemical mediators (neurotransmitters, cytokines, peptides) released from neighbouring nerves, inflammatory cells, interstitial cells and blood vessels. For example, urothelial membrane transport via ENaC is influenced by urine volume and composition, and is believed to mediate releases ATP from the urothelium to activate downstream sensory pathways [19].

2.2.3 Release of Mediators from the Urothelium to Transduce the Sensory Information

The most important substance released from the urothelium is ATP when the bladder is subjected to pressure changes or other signals such as altered pH and osmolality.

The urothelium also releases other agents such as acetylcholine, nitric oxide, substance P, and prostaglandins in response to stimuli such as stretch and chemical agonists [19, 57–59]. These chemical mediators can transduce a variety of sensory inputs into activation of sensory nerves and other cell types by acting on their corresponding receptors in a paracrine manner.

2.2.4 Expression of Sensory Receptors on the Sensory Nerves to Receive Chemical Signals from the Urothelium/Suburothelium

Diffusible urothelial mediators activate the underlying afferent nerves and other structures in a paracrine manner to contribute to bladder sensations. Several receptors may mediate

downstream steps from ATP release to activation of afferents, including purinergic ($P2X_3$) [21] and vanilloid (VR-1) [25] types. These receptors have been identified on urothelial and suburothelial nerve endings. In $P2X_3$ knock-out mice, distension-induced bladder afferent firing was attenuated and micturition reflex sensitivity was reduced [21, 22], supporting the functional role of P2X receptor in transducing chemical signal to afferent activity. Vanilloid receptor mediated mechanisms are also implicated as a suppressed micturition reflex also follows VR-1 knockout [60], and this may be particularly relevant to the transduction of chemical and thermal stimuli under inflammatory conditions. However, many intermediary steps are unknown; in particular, if ATP simply diffuses from release sites to afferent nerves, or if intermediate steps are also involved. There remains to be investigated what receptors on the sensory nerve to respond to other urothelium-derived substances.

2.2.5 Regulation of Urothelial Mediator Release by Neurotransmitters

The release of mediators from the urothelium can be regulated by other neurotransmitters. ATP is a major mediator released from the urothelium and its release from the urothelium has been studied by a number of investigators using cultured urothelial cells. Recent experiments from native urothelial tissue demonstrate that ATP release from the urothelium can be regulated by muscarinic and purinergic neurotransmitters [61]. This mode of action can be shown in both animal tissues and human tissues. Vesicular release, connexin conducting pathways and intracellular Ca^{2+} are differentially involved in these neurotransmitter-augmented urothelial ATP release. Of great interest, M2 receptors and P2Y receptors are the functional receptors for these effects. This is in contrast to the underlying smooth muscle, where M3 and P2X receptors control muscle contractions. Similar mode of action may also exist for the release of other urothelium-derived mediators. As acetylcholine and ATP are released from the urothelium itself they can act in an autocrine manner to amplify the chemical signal. Controlling sensory mediator release from the urothelium by other neurotransmitters thus represents a complex mechanism to fine-tune the sensory signalling.

2.2.6 Other Special Properties of the Urothelium

A recent study suggests that the urothelial tissue expresses functional clock genes and, in connection with detrusor muscle, exhibits circadian rhythms [62]. The daily rhythm of clock gene PER2 follows an approximate 24 h cycle with a peak around 12th hour (Fig. 2.1). The functional relevance is demonstrated by the fact that the contractile response to muscarinic agonist also exhibits similar circadian changes. Of particular interest, the clock activity can be modulated by the major bladder neurotransmitters—muscarinic and purinergic activators (Fig. 2.2). The local clock appears to reciprocally

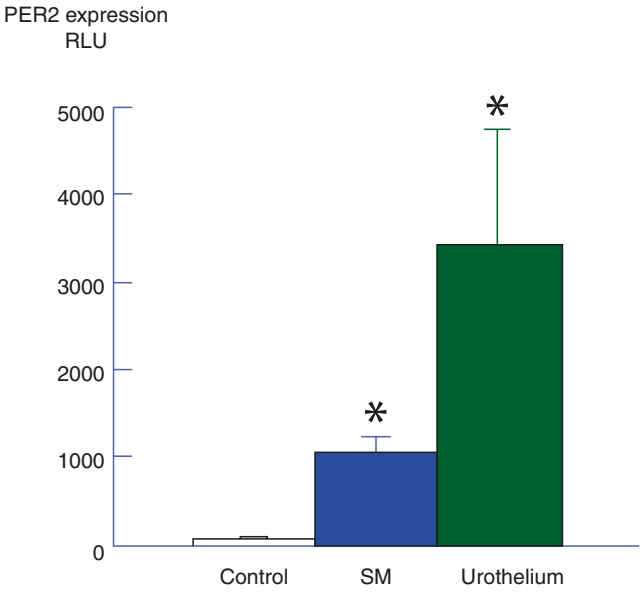

Fig. 2.1 Expression of clock protein PER2 in the urinary bladder from *PER2::Luc* knock-in mice. PER2 expression was measured by luminescence emission of the reporter gene luciferase and expressed as relative light unit (RLU). Data are expressed as Mean ± SEM from *PER2::Luc* mice bladders vs. wild-type (C57BL/6J) controls; *p < 0.05 vs. control; Expression of PER2 was detected in both detrusor muscle (SM) and the urothelial mucosa from *PER2::Luc* knockin mice

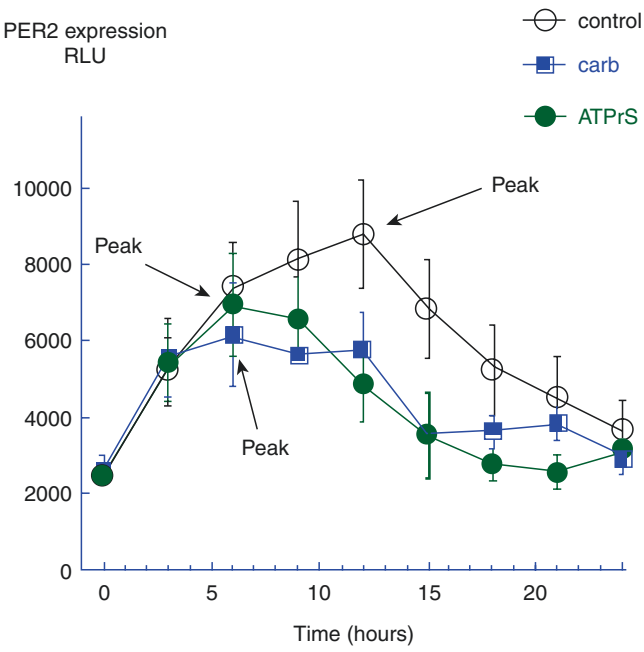

Fig. 2.2 Effect of neurotransmitter receptor agonists on PER2 activity in bladder tissue from *PER2::Luc* mice. 24-h changes of PER2 activity in control tissue and in the presence of muscarinic activator carbachol (10 μM) and purinergic activator ATP-γ-S (10 μM)

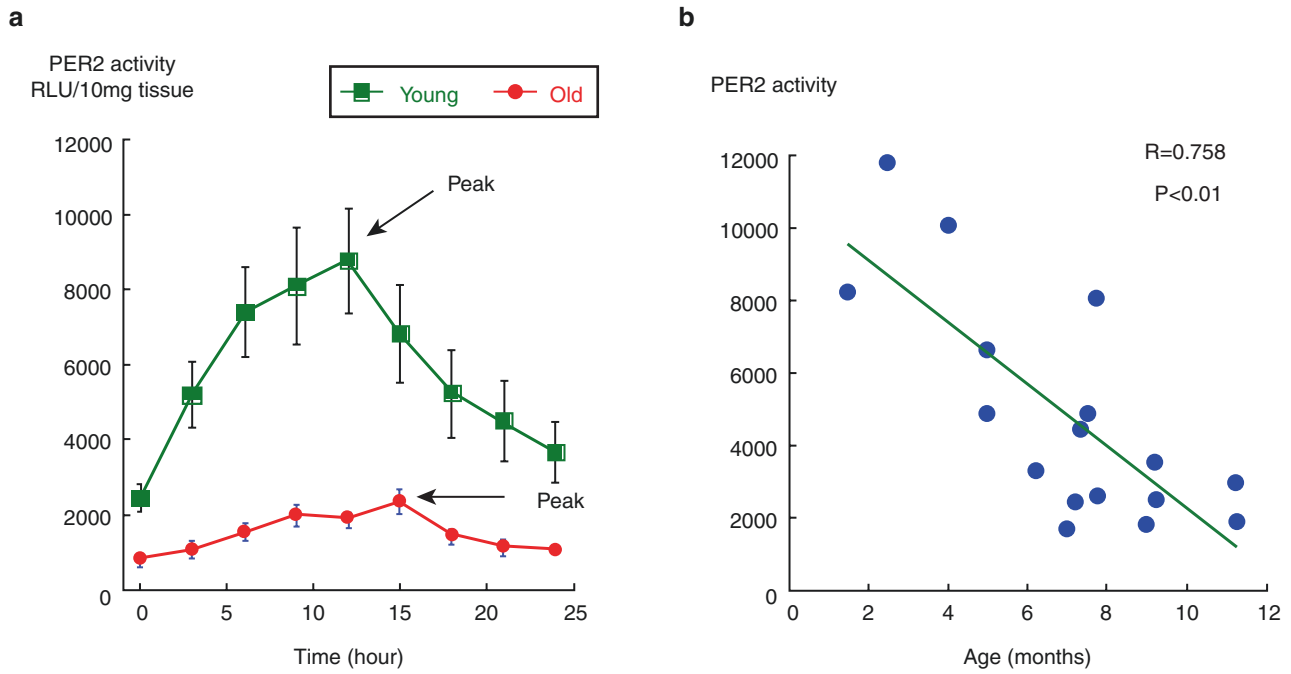

Fig. 2.3 Diurnal activity of PER2 expression in *PER2::Luc* mice and effect of age. (**a**) Changes of PER 2 activity of the bladder tissue in a 24 h cycle and age-dependence; PER2::luc mice; 3–5 month old vs. 9–12 month old. Note: a change in magnitude and peak time ($p < 0.05$). (**b**) Correlation of PER2 expression with age in *PER2::Luc* mice

align receptor activity to circadian rhythm for muscle contraction. The interaction between the down-stream receptors and peripheral clock represents an important mechanism for maintaining physiological function in bladder and other visceral organs in general. Furthermore, the clock expression is reduced in ageing tissue and the strength of this rhythm is also weakened (Fig. 2.3). Given the altered diurnal patterns of urination and nocturia seen in overactive bladder patients, this attenuation of normal time-setting system may favour uncontrolled spontaneous activities and detrusor instability.

Another recent study shows that urothelium releases high mobility group box-1 proteins which are responsible for causing non-inflammatory bladder pain. The release of this mediator from the urothelium is mediated by Toll-like receptor 4 [63].

These data suggest that urothelial bladder clock and Toll-like receptor 4 are new forms of regulators for bladder function and could be potential targets for therapeutic intervention.

2.3 The Pathological Significance of the Urothelium in Bladder Function

2.3.1 Alterations in Urothelium During Ageing

Ageing is a key risk factor that subjects the bladder prone to overactivity. Age-dependent, uninhibited detrusor contractions are a feature of both humans and animals and altered bladder sensation may be a feature of ageing. Although sensory function tends to decline with age in many systems, pelvic visceral sensory innervation is relatively resistant, as evidenced by no changes to CGRP-positive nerves [64]. Age-dependent morphological changes to urothelium have been observed [65, 66]. Functional changes to the urothelium also occur during ageing. There is an age-dependent increase of stretch-sensitive non-neuronal acetylcholine release from urothelium [59, 67, 68]. This increased acetylcholine release is also seen with bladder outflow obstruction. Spontaneous release of ATP is also increased in ageing urothelium [61]. These factors may contribute the high prevalence of overactive bladder symptoms in the elderly population. Thus urothelium signalling is likely to hold the key to understanding age-dependent changes in sensory function.

2.3.2 Alterations to Urothelium in Pathological Conditions

The urothelium and associated tissues are plastic and subject to physiological and pathological influences. Changes to the structure and function of the urothelium and sub-urothelium occur in pathological bladders from both animal models and human patients, including overactive bladders.

The barrier function can be compromised by many pathological factors as discussed in Sect. 1. Consequently, toxic and irritant urinary constituents can pass through the

epithelium and lead to changes in sensory pathways. The main mechanism is considered to be the action of the leaked sensory mediators on the underlying afferent fibres. A recent study provides direct experimental evidence that dysfunction of tight junction barrier by overexpression of claudin 2, a tight junction-associated protein which is significantly upregulated in biopsies of painful bladder patients, sensitises bladder afferent activity [69].

Inflammation may alter the response of urothelial cells to nociceptive and non-nociceptive stimuli. Increased sensitivity of the urothelial cells can be triggered by extracellular inflammatory mediators (ATP, NO, nerve growth factor, histamine, serotonin, adenosine, PGE2) released by sensory neurons and non-neuronal cells in the tissue compartments [70]. ATP is an important inflammatory mediator released from various cell types, and can initiate sensation of pain by exciting purinergic (P2X) receptors on sensory fibres. ATP can also potentiate the response of vanilloids by lowering the threshold for protons capsaicin and heat. This represents a novel mechanism whereby a large amount of ATP released from damaged/sensitized cells in response to inflammation may trigger the sensation of pain. In addition, there is evidence that inflammation may increase endogenous nerve growth factor and nerve growth factor may the link between tissue damage and hyperalgesic responses.

Changes to the urothelium have also been demonstrated in several clinically-important pathologies of the bladder. In painful bladder patients, ATP release from the urothelium is increased and the urothelial response to ATP is also upregulated [71, 72], aggravating the sensory disorders. In animal models of interstitial cystitis, the expression of P2X and P2Y receptors on the urothelial cells is altered, and stretch-induced ATP release from the urothelium is also increased [46, 73]. In human bladder overactivity, ATP release from the urothelium is increased and muscarinic receptor expression is reduced [74–76]; in suburothelial layer, connexin 43 expression on myofibroblasts is upregulated and P2X or TRPV1-postivie nerve fibres are increased [77–79], augmenting sensory transduction. In animal model of outlet obstruction-induced bladder overactivity, there is significant increase of M2 and M3 expression on the urothelium [80]. In animal model of spinal cord injury, augmented mucosal driven spontaneous smooth muscle activity has been demonstrated, providing evidence for mucosa-smooth muscle synergy in driving smooth muscle overactivity [44, 81]. Increased ATP release from the urothelium, which involves intracellular bacterial colonization, may play a role in the heightened symptoms associated with pyuric overactive bladder patients [82].Thus the urothelium is importantly involved in the pathogenesis of bladder disorders.

2.3.3 Urothelium as a Specific Target Tissue for Bladder Dysfunction

The urothelium has distinct receptor profiles which differ from the underlying smooth muscle [34, 45, 46, 61]. The urothelium expresses both P2Y receptors and P2X receptors while in the detrusor smooth muscle P2X receptors are abundant with limited P2Y expression. The main purinergic receptor for urothelial ATP release is P2Y, while in detrusor muscle P2X receptor is responsible for smooth muscle contractions. Furthermore, M2 receptor is mainly responsible for muscarinic activator-induced ATP release from the urothelium. In contrast, M3 is the functional receptor for the smooth muscle contractions. These special pharmacological properties provide the possibility for specific drug intervention in the urothelium with little effect on smooth muscle function.

Acknowledgement The author acknowledges the support from Biotechnology and Biological Sciences Research Council (BBSRC) (BB/P004695/1) and National Institute of Aging (NIA, 1R01AG049321-01A1).

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Peripheral Neural Control of the Lower Urinary Tract

3

Yasuhiko Igawa

3.1 Efferent Pathways of the Lower Urinary Tract (Fig. 3.1 [1])

The functions of the lower urinary tract to store and periodically evacuate urine are dependent upon neural circuitry in the brain and spinal cord [2–6]. Storage and elimination of urine are dependent upon the coordinated activity of two functional units in the lower urinary tract: (1) a reservoir (the urinary bladder) and (2) an outlet, consisting of bladder neck, urethra and striated muscles of the external urethral sphincter (rhabdosphincter) [7]. These structures are innervated by three sets of peripheral nerves: sacral parasympathetic (pelvic nerves), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain) and sacral somatic nerves (pudendal nerves).

3.1.1 Sacral Parasympathetic Efferent Pathways

The sacral parasympathetic outflow provides the major excitatory input to the urinary bladder. Cholinergic preganglionic neurons located in the intermediolateral region of the sacral spinal cord [8, 9] send axons via the pelvic nerves to ganglion cells in the pelvic plexus and in the wall of the bladder. This is an important fact to remember because patients with cauda equina or pelvic plexus injury are neurologically decentralized but may not be completely denervated. Cauda equina injury allows possible afferent and efferent neuron interconnection at the level of the intramural ganglia. The ganglion cells in turn excite bladder smooth muscle via the release of cholinergic (acetylcholine) and non-adrenergic, noncholinergic transmitters (ATP and others) and also inhibit urethral smooth muscle via the release of nitric oxide [7].

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3.1.2 Thoracolumbar Sympathetic Efferent Pathways

Sympathetic pathways to the lower urinary tract that originate in the lumbosacral sympathetic chain ganglia as well as in the prevertebral inferior mesenteric ganglia pass to the bladder via the hypogastric [10] and pelvic nerves [11]. Sympathetic efferent pathways elicit various effects including: (1) inhibition of detrusor muscle, (2) excitation of the bladder base and urethra [7] and (3) inhibition and facilitation in bladder parasympathetic ganglia [12–14].

3.1.3 Sacral Somatic Efferent Pathways

The efferent innervation of the urethral striated muscles originates from cells in a circumscribed region of the lateral ventral horn that is termed ‘Onuf’s nucleus’. Sphincter motoneurons send their axons through the pudendal nerves and excite sphincter muscles via the release of acetylcholine [15].

3.2 Efferent Neurotransmission

Parasympathetic postganglionic fibers terminate predominantly at the detrusor muscle and release ACh, resulting in detrusor contraction during voiding. Studies in animals have shown that sympathetic postganglionic fibers release noradrenaline (NA) and contribute to bladder relaxation during storage (via stimulation of β-adrenergic receptors expressed in detrusor).

3.2.1 Cholinergic Mechanisms

The vesicular acetylcholine transporter (VAChT) is considered a specific marker for cholinergic nerve terminals [16]. The muscle coat of the bladder showed a rich cholinergic innervation, and small VAChT-immunoreactive neurons

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_3

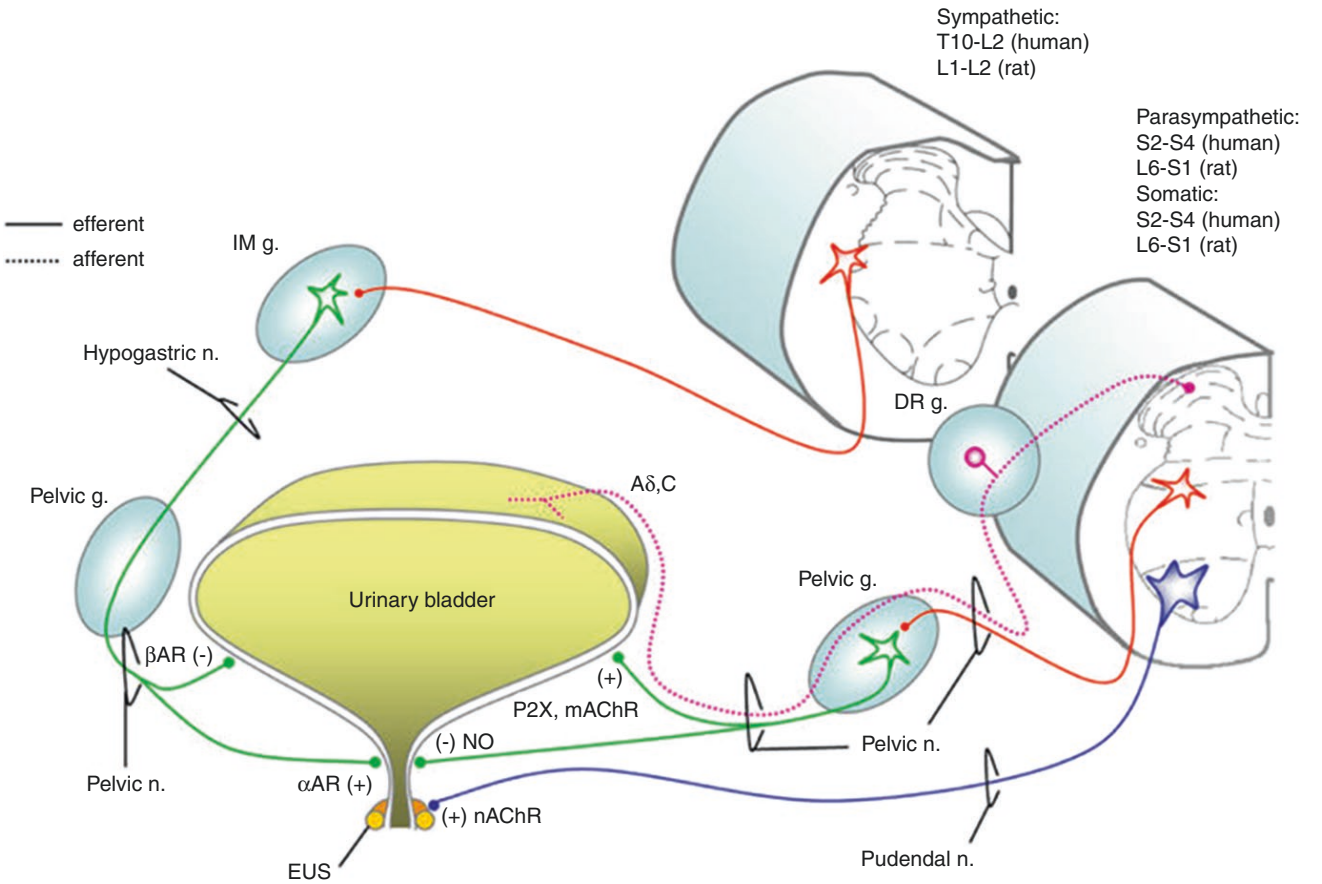

Fig. 3.1 Innervation of the lower urinary tract (LUT). The LUT is comprised of the bladder, urethral sphincter and urethra. The LUT receives the bulk of its innervation from three nerves. The hypogastric nerve carries sympathetic innervation to the LUT; contributing spinal nerves exit the spinal cord (SC) between L1 and L2. Muscle activity for storage is mediated by α-AR expressed in the trigone, bladder neck and urethra (excitatory), and by β-AR expressed in the bladder dome (inhibitory). The pelvic nerve contains parasympathetic input originating in the sacral cord (L6–S1 in rat) and controls micturition via cholinergic muscarinic receptors (mAChR) expressed throughout the LUT. The human pudendal nerve exits the sacral SC, and provides somatic innervation to the striated muscles of the external urethral sphincter; in rats, the pudendal nerve originates in the L6–S1 cord. In addition to their efferent function, each of these nerves carries afferent input from the LUT. Information about bladder distension is carried by mechanosensitive afferents (Aδ, C) found primarily in the pelvic nerve. These afferents signal the coordinated switch between storage and micturition. *Abbreviations*: *AR* adrenergic receptors, *DR g* dorsal root ganglion, *EUS* external urinary sphincter, *g* ganglion, *IM g* inferior mesenteric ganglion, *L* lumbar spinal cord, *mAChR* muscarinic cholinergic receptors, *n* nerve, *nAChR* nicotinic cholinergic receptors, *NO* nitric oxide, *P2X* purinergic receptor, *S* sacral spinal cord, (+) denotes excitatory synapses, (−) denotes inhibitory synapses

were found scattered throughout the detrusor muscle. VAChT-immunoreactive nerves were also observed in a suburothelial location in the bladder [17]. Muscarinic receptors comprise five subtypes, encoded by five distinct genes. The five gene products correspond to pharmacologically defined receptors, and M1 through M5 are used to describe both the molecular and pharmacological subtypes. In the human bladder, the mRNAs for all muscarinic receptor subtypes have been demonstrated [18], with a predominance of mRNAs encoding M2 and M3 receptors [18, 19]. These receptors are also functionally coupled [20–22]. Also, in most animal species, detrusor smooth muscle contains muscarinic receptors of the M2 and M3 subtypes [20–22].

The M3 receptors in the human bladder are believed to be the most important for detrusor contraction and to cause contraction through phosphoinositide hydrolysis [23, 24]. The main pathway for muscarinic receptor activation of the detrusor via M3 receptors is assumed to be calcium influx via L-type calcium channels, and increased sensitivity to calcium of the contractile machinery produced via inhibition of myosin light-chain phosphatase through activation of Rho-kinase [25].

The functional role for the M2 receptors has not been clarified, but it has been suggested that M2 receptors may oppose sympathetically mediated smooth muscle relaxation, mediated by β-ARs [26]. In certain disease states, M2 receptors may contribute to contraction of the bladder.

Thus, in the denervated rat bladder, M2 receptors or a combination of M2 and M3 mediated contractile responses, and the two types of receptor seemed to act in a facilitatory manner to mediate contraction [27–29]. In obstructed, hypertrophied rat bladders, there was an increase in total and M2 receptor density, whereas there was a reduction in M3 receptor density [30]. The functional significance of this change for voiding function has not been established. Pontari et al. [31] analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from M3 to the M2 receptor subtype, as found in the denervated, hypertrophied rat bladder. They concluded that whereas normal detrusor contractions are mediated by theM3 receptor subtype, in patients with neurogenic bladder dysfunction, contractions can be mediated by the M2 receptors.

Muscarinic receptors are also located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as M2 in the rabbit [32, 33] and rat [34], and M4 in the guinea pig [35], rat [36], and human [37] bladder. Prejunctional facilitatory muscarinic receptors appear to be of the M1 subtype in the rat and rabbit urinary bladder [32–34]. Prejunctional muscarinic facilitation has also been detected in human bladders [38]. The muscarinic facilitatory mechanism seems to be up-regulated in hyperactive bladders from chronic spinal cord-transected rats. The facilitation in these preparations is primarily mediated by M3 muscarinic receptors [38, 39].

3.2.2 Adrenergic Mechanisms

The body of the bladder receives a relatively sparse innervation by noradrenergic nerves. The density of noradrenergic nerves increases markedly toward the bladder neck, where the smooth muscle receives a dense noradrenergic nerve supply, particularly in the male [40]. Noradrenergic nerves also occur in the lamina propria of the bladder, only some of which are related to the vascular supply. Their functional significance remains to be established [40].

In the human detrusor, β -ARs dominate over α-ARs, and the normal response to noradrenaline is relaxation [41]. Goepel et al. [42] found that the number of α-ARs in the human detrusor was low, the order of abundance being β > α2> > α1. The amount of α1-ARs was too small for a reliable quantification [43]. Even if the α-ARs have no significant role in normal bladder contraction, there is evidence that this may change after, for example, bladder outlet obstruction, parasympathetic decentralization, and in overactive bladders.

The relaxant effect of noradrenaline on the detrusor can be exerted both pre- and postjunctionally [44]. Stimulation of α2-ARs on cholinergic neurons may lead to a decreased release of acetylcholine. Since β-ARs dominate over α-ARs postjunctionally in the bladder [41, 43], noradrenaline relaxes the detrusor through stimulation of β-ARs. β-AR agonists are considered to stimulate adenylyl cyclase to increase cAMP. In turn, cAMP activates protein kinase A to mediate the biological effects. Both normal and neurogenic human detrusors are able to express β1-, β2-, and β3-AR mRNAs, and selective β3-AR agonists effectively relaxed both types of detrusor muscle [45–48]. Thus, it seems that the β-AR-mediated response in the human bladder is mediated by β3-ARs. These findings would suggest β-AR, and particularly β3-AR, stimulation as a way of keeping the bladder relaxed during filling. However, this does not necessarily mean that this mechanism is active during normal filling. The importance of the sympathetic input for human bladder function is controversial. Sympathectomy has no distinct effect on bladder filling, and neither has blockade of β-ARs [49]. The sympathetic nervous system may not be essential for urine storage in humans. However, if released noradrenaline contributes to bladder relaxation during filling, it may be through stimulation of both β2- and β3-ARs.

3.2.3 Non-adrenergic, Non-cholinergic Mechanisms

In most mammalian species, part of the bladder contraction induced by electrical stimulation of nerves is resistant to atropine [41]. The proportion of non-adrenergic, non-cholinergic (NANC) -mediated response to the total contraction varies with species and the frequency of stimulation. The role of a NANC mechanism in the contractile activation of the human bladder is still disputed [41, 50]. Most probably, normal human detrusor muscle exhibits little “atropine resistance.” This does not exclude that atropine resistance may exist in morphologically and/or functionally changed bladders. Thus, the NANC component of the nerve-induced response may be responsible for up to 40–50% of the total bladder contraction in different conditions associated with detrusor overactivity [51–57].

3.3 Afferent Pathways of the Lower Urinary Tract (Fig. 3.1 [1])

Afferent pathways of the lower urinary tract consist of the three sets of nerves [58]. The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia (DRG), whereas afferent innervation in the

hypogastric nerves arises in the rostral lumbar DRG. The central axons of the DRG neurons carry the sensory information from the LUT to second-order neurons in the spinal cord [59–61]. These second-order neurons provide the basis for spinal reflexes and ascending pathways to higher brain regions involved in micturition, continence, and mediation of sensation [62]. The most important afferents for initiating micturition are those passing in the pelvic nerve to the sacral spinal cord. The Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of the bladder contraction. These afferents are small myelinated (Aδ) and unmyelinated (C) fibres, which convey information from receptors in the bladder wall [63–67] to second-order neurons in the spinal cord. The switch initiating voiding from the urine storage phase relies on sensory signals, which provide the input to the reflex circuits that control bladder filling and emptying and are also the source of both non-painful sensations of fullness and pain. Afferent signalling dysfunction leads to a number of disorders such as overactive bladder syndrome (OAB) and hypersensitive bladder disorders. The recent view that dysregulated afferent signaling rather than exaggerated bladder contractile properties are responsible for these storage disorders and therefore targeting afferent mechanisms may be a rational approach to treatment.

3.4 Properties of Bladder Afferent Neurons

A small proportion of DRG neurons supply bladder and urethra. Those supplying the bladder are pseudounipolar with a central projection into the dorsal horn of the spinal cord and a peripheral axon that terminates at different levels in the bladder wall. DRGs supplying pelvic and pudendal afferents originate in the thoracic, lumbar and sacral regions while hypogastric afferents arise mainly from the rostral lumbar dorsal root ganglia. The central projections of these DRG neurons carry the sensory information from the lower urinary tract to second order neurons in the spinal cord. The cell size of bladder DRGs is consistent with there being two populations of afferents with one connecting to small unmyelinated C-fibre afferents and the other to finely myelinated Aδ fibres. Aδ bladder afferents in the cat respond in a graded manner to passive distension as well as active contraction of the bladder and exhibit pressure thresholds in the range of 5–15 mmHg, which are similar to those pressures at which humans report the first sensation of bladder filling. These fibres also code for noxious stimuli in the bladder. On the other hand, C-fibre bladder afferents in the cat are insensitive to mechanical stimuli and commonly do not respond to even high levels of intravesical pressure [68]. However, activity in these afferents is unmasked by chemical irritation of the bladder mucosa. These findings indicate that C-fibre afferents in the cat have specialized functions, such as the signalling of inflammatory or noxious events in the lower urinary tract. In the rat, Aδ-fibre and C-fibre bladder afferents cannot be distinguished on the basis of stimulus modality; thus both types of afferents consist of mechanosensitive and chemosensitive populations [62]. During neuropathic conditions (spinal cord injury) and possibly inflammatory conditions, there is recruitment of C fibers that form a new functional afferent pathway that can cause urgency incontinence and possibly bladder pain.

In the urethra, afferent nerves have been reported between the muscle fibers, surrounding blood vessels, within the urothelium, and in a dense suburothelial plexus [69–71]. The striated sphincter muscle surrounding the urethra receives a very sparse afferent innervation that is localized primarily to nerve bundles passing between the muscle bundles. Specialized tension receptors (muscle spindles) that are innervated by large-diameter myelinated group IA afferents and that are prominent in most striated muscles are absent [72] or are present in low density [73] in striated sphincter muscles.

There are also reports that have identified and characterized functional properties of sacral afferents responding to flow through the urethra [74]. These are important observations whereby properties of these flow-responsive afferents seem to parallel those of cutaneous afferents. This could be important in terms of restoration of bladder emptying after spinal cord injury.

3.5 Urothelial Afferents

The urothelium can no longer be considered a passive barrier protecting against diffusion of urine constituents. Recent evidence suggests instead that the urothelium possesses sensory functions and may transduce mechanical and chemical stimuli to underlying structures including smooth muscle, fibroblast like cells, immune cells and bladder nerves including the terminals of afferents which are located in close proximity, or even within, the urothelium. The recent evidence supporting involvement of a number of these urothelially-derived factors in sensory signaling and the therapeutic potential of targeting these signaling pathways is considered below [75].

3.6 Modulation of Afferent Sensitivity

The relationship between stimulus and response is not fixed but can be changed according to the mechanical and chemical environment of the sensory ending. For example, chemicals released from a variety of cells within the bladder wall and particular the urothelium and lamina propria influence afferent firing. Many mediators are released during inflam-

mation, injury and ischemia, from platelets, inflammatory cells, fibroblasts, blood vessels, muscle and neurons. Some mediators act directly on sensory nerve terminals, while others act indirectly, causing release of yet other agents from nearby cells. The increased sensitivity to both mechanical and chemical stimuli may contribute to chronic pain states. Local mediators may include neurotrophins, amines, purines, prostanoids, proteases, and cytokines. They produce their effects on visceral afferent nerves by three distinct processes. First, they can act directly, by opening ion channels on the nerve terminals. Second, they can sensitize endings without causing direct stimulation but causing hyperexcitability to other chemical and mechanical stimuli. Third, as is the case with neurotrophins, they can change the phenotype of the afferent nerve over long periods. For example, they may alter expression of channels, receptors, or mediators in the sensory neuron [76].

3.7 Role of ATP and P2X3 Receptors in Bladder Sensation

ATP is a neuronally and non-neuronally released mediator in virtually every cell type; studies in the bladder actually have been pivotal in establishing ATP as an intercellular mediator [77]. Urothelial ATP release can be stimulated not only by stretch [75], but also by agonists at muscarinic receptors, bradykinin receptorsas and TRPV1 channels [78].

It is well established that the urothelium releases ATP in response to stretch and that this acts in a paracrine fashion to influence the function of myofibroblasts and bladder afferent nerves. P2X2 and P2X3 receptors are expressed on unmyelinated afferent fibres innervating the bladder. Mice lacking the P2X3 receptor showed reduced inflammatory pain and marked urinary bladder hyporeflexia with reduced voiding frequency and increased voiding volume, suggesting involvement of P2X3 receptors in mechanosensory transduction [79]. A P2X3 antagonist, AF-219, has been tested in a proof-of-concept trial in treating symptoms associated with bladder pain syndrome/interstitial cystitis (BPS/IC), which suggested the potential efficacy of P2X3 receptor antagonists for the treatment of BPS/IC [80].

3.8 Nitric Oxide (NO)

NO has been identified as a major inhibitory transmitter mediating relaxation of the urethral smooth muscle during micturition [25, 41, 81]. In addition, NO is also involved in controlling bladder afferent nerve activity.Several lines of evidence indicate that urothelial and suburothelial NO has a role in the micturition reflex pathway [75, 81, 82]. Birder et al. [82], using reverse transcription-PCR, showed that both inducible NO synthase (iNOS) and endothelial NOS (eNOS), but not neuronal NOS (nNOS) genes, were expressed in cultured rat urothelial cells. Gillespie et al. [83, 84] demonstrated that interstitial cells, lying immediately below the guinea pig urothelium, respond to NO with a rise in cGMP. They found a high degree of complexity in nNOS distribution and NO target cells in the lamina propria and suggested that this may reflect distinct physiological functions that have yet to be identified. Aizawa et al. [85] examined the effect of NO on sensory signaling by directly recording afferent activity arising from the rat bladder *in vivo*. Iintravenous administration of L-arginine, an NO substrate, decreased mechanosensitive primary bladder afferent activities of both Aδ- and C-fibers during saline instillation. Intravesical instillation of an NO synthase inhibitor (N(ω)-nitro-L-arginine methyl ester hydrochloride [L-NAME]) increased afferent activities of both fibers, wiich was inhibited by intreveous administration of L-arginine. In addition to studying NO mechanisms in the normal bladder, Aizawa and colleagues also showed that application of L-arginine inhibited hypersensitivity induced by the cyclophosphamide metabolite acrolein that is used experimentally as a model for BPS/IC [85]. The actions of NO are mediated through elevation of the intracellular second messenger cGMP [86]. The second messengers cAMP and cGMP are synthesized from the corresponding nucleoside triphosphates by their respective membrane-bound or soluble adenylate or guanylate cyclases. cAMP and cGMP are inactivated by phosphodiesterases (PDE) by hydrolytic cleavage of the 3′-ribose phosphate bond. Therefore, the level of intracellular second messengers can be regulated by PDE isoenzymes [87, 88]. For example, PDE type 5 inhibitors can be used therapeutically to prolong the action of NO by inhibiting cGMP-metabolism. Minagawa et al. [89] reported that tadarafil, a PDE type 5 inhibitor, reduces mechanosensitive afferent activities of both Aδ- and C-fibres elicited by bladder distension in the rat, and also that tadalafil has an inhibitory effect on the increased activities of both fibres induced by intravesical acrolein instillation, similarly as L-arginine. Taken together, these data suggest that NO-cGMG signaling pathways are involved in suppression of bladder mechanosensation and its hypersensitivity.

3.9 Transient Receptor Potential (TRP) Cation Channels

TRP channels constitute a large superfamily of cation selective channels. The human TRP family consists of 27 members that are divided in six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin) and TRPA (ankyrin) [90]. A particular characteristic of these ubiquitously expressed channels is

that a wide range of physical and chemical stimuli can regulate their activation. Thus, TRP channels can act as polymodal cellular sensors that are involved in numerous sensory and homeostatic processes [91]. A number of different members of the TRP channel family are expressed in the bladder mostly in association with sensory nerve fibers involved in mechanotransduction and nociception. TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1 have all been shown to be expressed in the bladder [91, 92].

3.9.1 TRPV1

TRPV1 is highly expressed in C-fibres innervating the urinary bladder and urethra in several mammals including rats, mice and humans [91]. TRPV1 has been shown to play an integral role in modulating the excitability of bladder afferents and the generation of hypersensitivity, induced by bladder inflammation [93, 94]. The functional role of TRPV1 in the bladder has been studied using TRPV1 knockout (KO) mice. Compared with wild-type littermates, These TRPV1 KO mice had a higher frequency of non-voiding bladder contractions and had reduced reflex voiding under anaesthesia compared to wild, but not in awake animals [93].Moreover, TRPV1 KO mice exhibit reduced firing of bladder afferents in response to bladder distension [95], indicating a facilitatory role for TRPV1 in bladder mechanosensory transduction. In several animal models of LUT dysfunction including bladder hyperactivity in mice with lipopolysaccharide (a bacterial toxin)-induced cystitis and in rats with neurogenic bladder overactivity after spinal cord injury, selective TRPV1 antagonists have proven to be promising candidates for drug therapy [91]. However, it became rapidly clear that TRPV1 antagonists cause an increase in body temperature (hyperthermia), both in animal models and in humans [91, 96].

3.9.2 TRPA1

As a mediator of inflammation and pain, TRPA1 is considered a potential target in the treatment of visceral hypersensitivity syndromes, e.g. inflammatory bowel disease and overactive bladder. TRPA1 is expressed in the bladder and is particularly associated with C-fiber endings in the suburothelium that co-localize CGRP. Agonists acting at the receptor cause bladder overactivity and is suggested to play a role in mechanosensory transduction and in signaling pain. A TRPA1 antagonist, HC030031, has been proven effective to ameliorate cystometric parameters in rats with bladder overactivity after spinal cord injury. In these rats, TRPA1 expression in DRG ganglia was upregulated at the protein and mRNA level and the effects of the TRPA1 antagonists could be mimicked by TRPA1 RNA knockdown [97]. In a visceral pain model, using cyclophosphamide-induced cystitis, HC030031 effectively alleviated cystitis induced bladder hyperalgesia [98]. Although these drugs show efficacy in various animal models for pain and hyperalgesia, they await clinical validation [99].

3.9.3 TRPV4

Functional TRPV4 expression has been shown in bladder urothelial cells in mice, rats, guinea-pigs and humans [91, 100]. TRPV4 is located predominantly on the surface of the basal urothelial cell layers, in close proximity to the adherence junctions [101]. *In vitro* experiments on cultured urothelial cells showed that cells from TRPV4 KO mice had attenuated Ca2+-influx and ATP release in response to stretch compared with cells from control mice [102]. Moreover, isolated TRPV4 KO mouse bladders showed reduced stretch-evoked ATP release [100]. *In vivo,* these KO mice exhibit less frequent voiding [100] and larger bladder capacity [103]. Moreover, intravesical infusion of GSK1016790A, a potent TRPV4 agonist is able to induce bladder hyperactivity in rodents [103, 104] and increased afferent firing of capsaicin-insensitive C-fibres in rats [104]. Furthermore, systemic administration of the TRPV4 antagonist HC067047 increases bladder capacity and reduces micturition frequency in a mouse model of cyxclophosphamide-induced cystitis [105]. These findings support the hypothesis that TRPV4 acts as a mechano-sensor in urothelial cells and activates the underlying C-fiber afferent nerves via ATP-release. Further, there is evidence that a co-administration of antagonists to both TRPV4 and TRPV1 can potentiate the effect of each drug and reduce bladder hyperactivity in a rodent model for cystitis [106]. Interestingly, no significant adverse effects of systemic treatment with the TRPV4 antagonists HC067047 and GSK2193874 have been reported in rodents [105, 107]. A protocol of the first Phase I clinical trial with a systemic TRPV4 antagonist (GSK2798745) has been recently published to test its safety and tolerability in healthy subjects and patients with stable heart failure. Results of this study are awaited eagerly [91].

3.9.4 TRPM8

TRPM8 is activated by cool temperatures (8–25 °C) and by chemicals that provoke ‘cool’ sensations, such as menthol and icilin. As a cold sensor in the body, TRPM8 is predominantly expressed in a small subpopulation of DRG and trigeminal neurones that do not express TRPV1 [108]. TRPM8 expression was shown in a subset of small nerve fibres in the human bladder [109] and DRG neurons innervating the rat bladder [110]. Lashinger et al. [111] showed that application

of AMTB, a TRPM8 channel antagonist inhibited isovlumetric bladder contractions and bladder nociceptive reflex responses in the rat, suggesting that in addition to cold sensing TRPM8 may also be involved in the afferent control of micturition and nociception. Systemic application of another TRPM8 antagonist, BCTC, reduces cold stress-induced bladder overactivity in rats [112]. A recent study by Ito et al. [113] also showed that TRPM8 have a role in activation of mechanosensitive C-fiber bladder afferent activity recordings in an ex vivo rat model. These experimental findings in animals propose TRPM8 antagonists as a promising therapeutic tool for overactive bladder and hypersensitive bladder disorders. However, systemic application of TRPM8 antagonists generally decreases deep body temperature (hypothermia) [113, 114], which may limit clinical trials.

3.10 Cannabinoids

It has been reported that the use of cannabis based extracts significantly improved symptoms of urge incontinence and detrusor overactivity in patients with multiple sclerosis [115, 116]. This observation has provoked interest in the study of expression and function of cannabinoid receptors in the bladder. Endogenous cannabinoids can potentially interact with TRPV1 but in addition can act on G-protein coupled cannabinoid receptors 1 and 2 (CB1, CB2). In the human bladder, both receptors could be identified in the urothelium and detrusor where CB1 receptors were more abundant than CB2 [117]. In patients with bladder pain syndrome and idiopathic detrusor overactivity (IDO), a significant increase in nerve fibres expressing CB1 in the urothelium was observed, strongly suggesting a role for CB1 in overactive bladder [118]. In contrast, Gratzke and colleagues [119] showed that CB2 receptors predominated in the urothelium, suburothelium and on sensory nerve fibres and found that CB2 agonists inhibited nerve induced contractions of the bladder, suggesting that CB2 receptors are important in micturition. Aizawa et al. [120] demonstrated using a peripherally restricted inhibitor (URB937) of the endocannabinoid-degrading enzyme fatty acid amidehydrolase (FAAH), that inhibiting peripheral FAAH depresses the Aδ and C-fiber activity of primary bladder afferents via CB1 and CB2 receptors. More recently, Aizawa et al. [121] reported that URB937, the peripherally restricted FAAH inhibitor, reduces bladder overactivity and C-fibre hyperactivity in the rat bladder provoked by PGE2, suggesting an important role of the peripheral endocannabinoid system in BO and hypersensitivity.upregulation of the peripheral endocannabinoid system reduces bladder overactivity and C-fiber hyperexcitability in the rat bladder provoked by PGE2, suggesting an important role of the peripheral endocannabinoid system in bladder overactive conditions induced by afferent hypersensitivity. Amplification of endocannabinoid activity by FAAH inhibitors may be an attractive drug target in specific pathways involved in LUTS [122].

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Spinal Cord

4

Mitsuharu Yoshiyama and Hidehiro Kakizaki

4.1 Spinal Projections of Lower Urinary Tract Primary Afferent Neurons

Spinal reflex circuitry controlling lower urinary tract function comprises four basic components, which are primary afferent neurons, interneurons, efferent neurons, and axonal projections from neurons in the brain that have synaptic connections with these spinal neurons. The spinal cord receives sensory information such as bladder fullness or bladder pain via afferent axons in the pelvic and hypogastric nerves and the dorsal root ganglia at the S_2-S_4 and T_{11}-L_2 segmental levels, respectively, which contain somata of these afferent nerves in humans. Impulses from tension receptors and nociceptors in the bladder wall are carried via afferent fibers to neurons in the dorsal horn of the spinal cord. Lissauer's tract at the apex of the dorsal horn receives projections of the pelvic nerve afferent pathways from the urinary bladder and sends them rostro-caudally, with collaterals that extend laterally and medially through the superficial layer of the dorsal horn (lamina I) into deeper layers at the base of the dorsal horn (laminae V–VII and X) (Fig. 4.1) [1–4]. The lateral pathway with the most significant projection terminates in the region where the sacral parasympathetic nucleus is located and sends some axons to the dorsal commissure. No bladder afferents are determined in the center of the dorsal horn (laminae III–IV) or in the ventral horn. In cats, there are similar sites in laminae I, V–VII, and X in which sympathetic afferents via hypogastric nerves from the pelvic viscera to the rostral lumbar segments terminate [5]. Distribution of the afferents is prominent primarily in the ipsilateral side of the spinal cord that partially project to the opposite side (≈20%) [6, 7]. Pudendal nerve afferent pathways including those of the external urethral sphincter centrally terminate at S_2-S_4 spinal segments in humans that partially overlap with those of bladder afferents in the lateral laminae I, V–VII, and X [8–10]. These afferents are prominently different from other populations of pudendal nerve afferents that innervate sex organs and cutaneous and subcutaneous tissues of the perineum, those of which terminate in deeper layers of the dorsal spine (laminae II–IV) [10–12].

4.1.1 Effects of Afferents from the Urethra, Bowel and Genital Organs on Parasympathetic Activity

Afferent signals from the pelvic viscera are conveyed to the dorsal root ganglia and further to the dorsal horn of the spinal cord primarily via hypogastric, splanchnic, pelvic, and pudendal nerves [13]. These nerves transmit sensory information from the major pelvic organs, including the urinary bladder, urethra, colon, rectum, and genitalia (Fig. 4.2) [14]. Convergence of sensory information mediates viscero- and somato-visceral reflexes and interactions between urinary, gastrointestinal, and reproductive systems via both the peripheral and central mechanisms of afferent signal processing. Central mechanisms include structures in the spinal cord and the brain, and major peripheral mechanisms involve the sensory fibers and the cell bodies of sensory neurons localized within the dorsal root ganglia [15, 16].

Visceral pain often leads to secondary visceral hyperalgesia, somatic hyperalgesia or both, which is usually explained by the spinal convergence-projection theory. An irritated pelvic organ sends augmented afferent impulses that sensitize viscerovisceral convergent neurons within the spinal cord and enhance the impact of afferent inputs from neighboring organs (Fig. 4.3) [13, 16]. The proportion of neurons in the

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_4

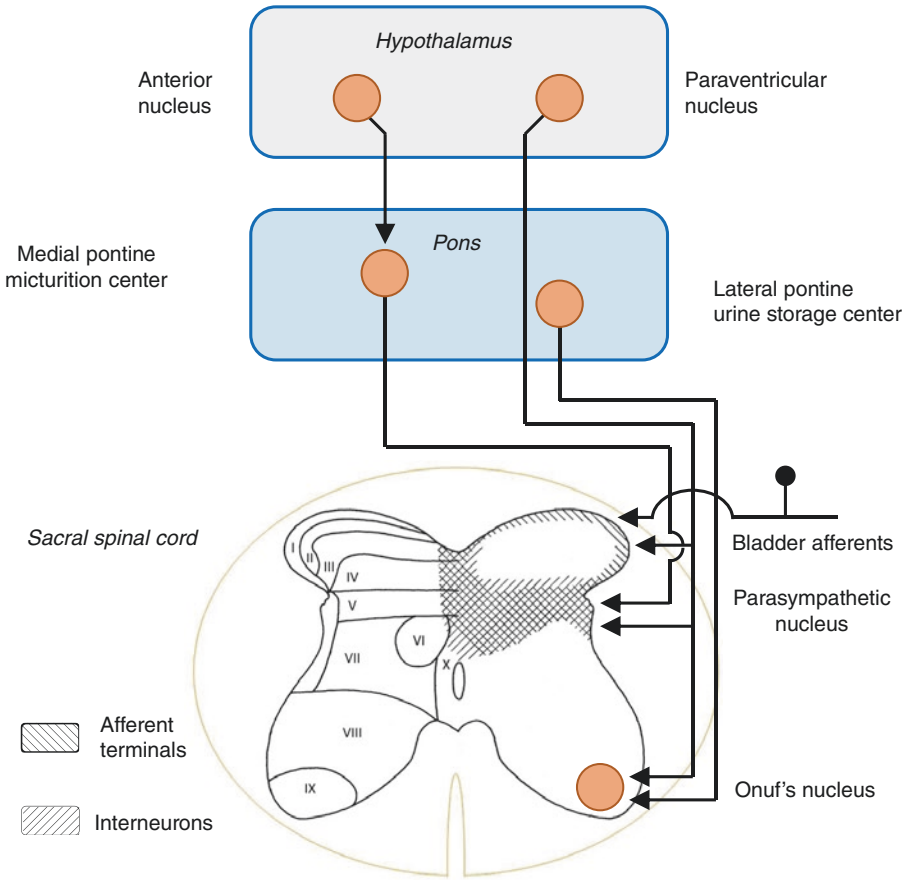

Fig. 4.1 Schematic showing the neural circuitry between the supraspinal and the sacral spinal cord regulating lower urinary tract function in cats. Terminals of descending pathways from the medial pontine micturition center, the lateral pontine urine storage (or sphincter center), and the paraventricular nuclei of the hypothalamus project onto the sacral spinal cord

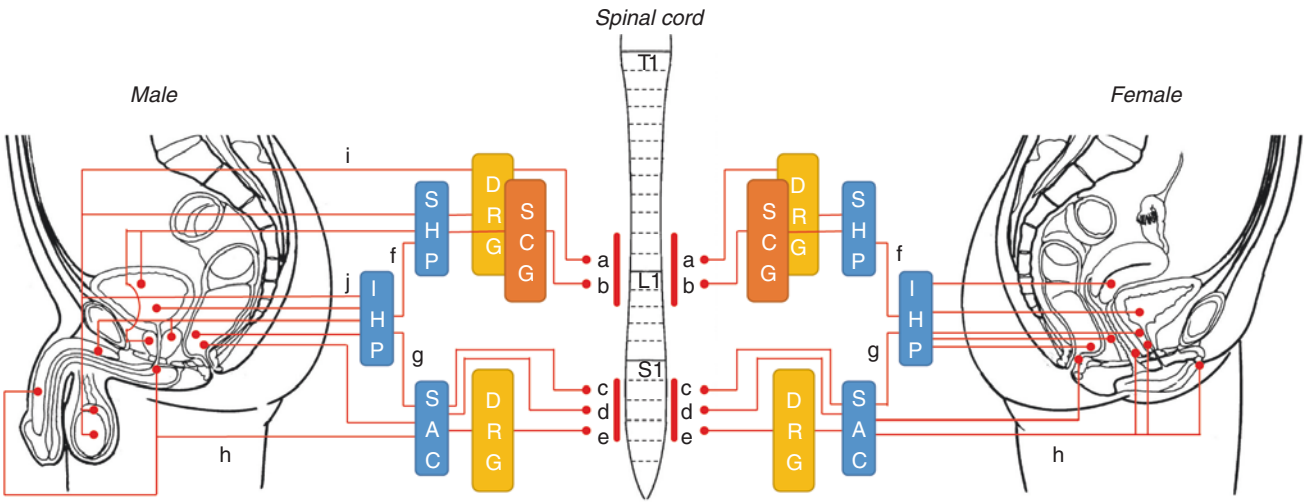

Fig. 4.2 Schematic showing the innervation of the urogenital and rectal areas in males and females. The anatomical descriptions are largely derived from animal studies [17] although human structures are presented in the diagram to show the innervation. Each label indicates the following: *a* input to afferent neurons in the dorsal horn; *b* input to intermediolateral region (sympathetic neurons); *c* sphincter motor neurons; *d* input to intermediolateral region (parasympathetic neurons); *e* input to afferent neurons in the dorsal horn; *f* hypogastric plexus; *g* pelvic splanchnic nerve; *h* pudendal nerve; *i* superior spermatic plexus; *j* inferior spermatic plexus. *IHP* inferior hypogastric plexus; *SAC* sacral plexus; *SHP* superior hypogastric plexus

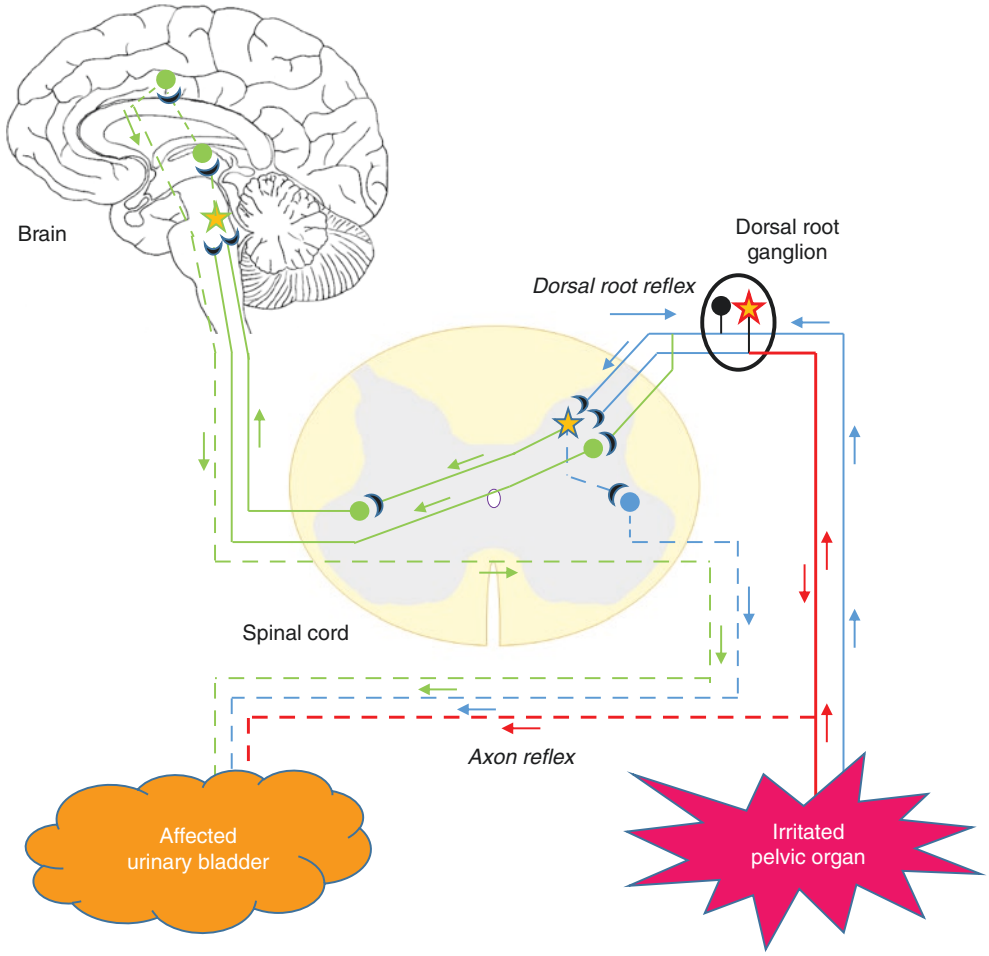

Fig. 4.3 Schematic representing the convergent afferent pathways. The red route indicates a convergence of sensory neural pathways within a dorsal root ganglion (DRG). Dichotomizing afferents by an axon-reflex mechanism that induces antidromic propagation of an action potential from a DRG to the periphery contributes to propagation of a noxious stimulus from an irritated pelvic organ to the urinary bladder. The blue route indicates a convergence of afferent signals in the spinal cord. Antidromic conductance via sensory fibers from the spinal cord to the periphery induces the dorsal root reflex. The green route indicates a convergence of afferent inputs from two different pelvic organs in the brain. A star symbol indicates convergent neurons in the DRG, the spinal cord, and the brain. Solid lines and arrows in respective color for each route draw orthodromic propagation of an action potential from the pelvic organs to the convergent point. Dotted lines depict an anterograde action potential propagation from the brain, the spinal cord, and DRG to the periphery

spinal cord that receive convergent input from two or more pelvic organs is higher than that of dorsal root ganglion cells that innervate multiple viscera [18, 19]. The greater abundance of convergent neurons in the spinal cord likely suggests that a central amplification process is important in cross-organ sensitization. Possible mechanisms that mediate referred visceral pain or viscerovisceral cross-organ sensitization in the pelvis are the following: antidromic axon reflexes via a single primary afferent supplying two (dichotomizing) structures (pre-spinal convergence), afferent–afferent interactions via spinal interneurons or overlapping terminal fields in the spinal cord (convergence-projection), supraspinal mechanisms, sympathetic reflexes, and cross-sphincteric reflexes [20].

4.1.1.1 Urethra

The urethra receives innervation from pudendal, pelvic, and hypogastric nerves.

Of these, the sensory axons of the pudendal and pelvic nerves transmit afferent signals to the lumbosacral spinal cord in response to urethral distension [21]. Distension of or fluid flow through the urethra causes excitation of the pudendal nerve afferents and activates a reflex that augments ongoing bladder contraction in humans [22]. However, the elicitation of bladder contraction by fluid flow through the urethra is achieved only when the bladder volume is sufficiently large. Conversely, when the bladder volume is small, the flowing fluid through the urethra inhibits bladder activity. The volume dependency is mediated by the convergence of a

deep perineal afferent (i.e., a caudal branch of the pudendal nerve) and a bladder stretch afferent (i.e., the pelvic nerve) within the spinal micturition circuitry that modulates the urethra-to-bladder reflexes [22].

Low-frequency electrical stimulation of an afferent axon of the pudendal nerve in humans or the deep perineal nerve in cats activates bladder preganglionic parasympathetic neurons in the spinal cord and initiates reflex bladder contractions and voiding [23]. The micturition reflex also can be achieved if the bladder contains a sufficient volume. Additionally, stimulating the somatic afferents in the pudendal nerve from the external urethral sphincter to the lumbosacral spinal cord suppresses the micturition reflex.

Stimulation of the pudendal nerve can activate the hypogastric nerve fibers, which suppress an excitatory pelvic efferent outflow to the bladder on the ganglion level [24]. A gating mechanism in the spinal cord can direct the pudendal afferents to influence either the pelvic or the hypogastric efferent. Alternatively, the pudendal nerve may have access to both pelvic and hypogastric neurons and regulate the ongoing bladder activity, depending on the intravesical volume or pressure.

Urethral anesthetization or blocking activity of urethral afferents in healthy humans results in incomplete emptying and the necessity to strain [25, 26]. Thus, the urethra-to-bladder (or the urethrovesical) augmenting reflex provides sensory feedback from the urethra during urine flow and contributes to efficient voiding. Interestingly, introducing a noxious stimulus (capsaicin) into the urethra produces marked inhibition of urinary bladder activity in rats [27]. This result suggests that urethral irritation elicits an inhibitory urethrovesical reflex.

4.1.1.2 Bowel

Stimulation of the anal canal or rectum may inhibit urinary bladder motility, and these effects are assumed to be modulated by a central mechanism involving pelvic nerve afferents and by a peripheral adrenergic system via the hypogastric nerves that may have a role in the inhibitory rectovesical reflex [28]. Non-noxious colorectal distension leads to inhibition of the micturition reflex, whereas spontaneous colonic motility is inhibited during micturition, thus indicating that normally micturition and defecation occur alternately.

Distension of the colon and anus increases periurethral muscle electrogram activity without affecting bladder tone if the bladder pressure is low in rats [29]. In contrast, if the bladder is full, such stimuli reduce the size and frequency of bladder contractions, which is related to reduced pelvic nerve efferent activity and produces a simultaneous decrease in periurethral muscle electromyogram activity. The findings of the bladder being filled are attributable to reductions in the rate of discharge in nerve fibers, most of which belong to the parasympathetic system, and in the rate of action potentials of the pudendal efferent nerve activity. Thus, central projections overlapping with pelvic and pudendal afferents facilitate integration of parasympathetic and somatic motor activity in the pelvis and activate the orchestration of the sacral reflexes. The pudendal nerve also makes innervation to the muscle and skin in the perianal area. Activation of the pudendal afferent nerve fiber by perianal electrical stimulation induces frequency-dependent reflex responses of the bladder in conscious cats with chronic spinal cord injury [30].

Patients who suffer from irritable bowel syndrome frequently present with signs of hypersensitive urinary bladder, encompassing urinary frequency and urgency, nocturia and incompleteness of bladder emptying. Urodynamic studies of irritable bowel syndrome patients reveal detrusor instability and suggest that irritable bowel syndrome may lead to urinary storage dysfunction [31]. Moreover, irritable bowel syndrome often overlaps with interstitial cystitis and occurs concomitantly. Approximately 40–60% of patients diagnosed with irritable bowel syndrome have symptoms of and fulfill diagnostic criteria for interstitial cystitis, whereas approximately 38–50% of patients diagnosed with interstitial cystitis exhibit symptoms of and fulfill diagnostic criteria for irritable bowel syndrome [32–35].

Acute colonic inflammation in rats significantly enhances excitation in response to urinary bladder distension in convergent spinal neurons responding to both colorectal distension and urinary bladder distension [19]. In experimental colitis, pelvic organ cross-sensitization leads to urinary bladder hyperalgesia with no detectable histological changes in the urinary bladder wall.

The underlying mechanism for the hyperalgesia is thought to involve the sensitization of intraspinal neurons and appropriately expound the clinical manifestations of viscerovisceral referred pain in patients with irritable bowel syndrome or interstitial cystitis.

In rats, inputs from both the urinary bladder and colon converge on 32% of L_6-S_2 spinal neurons [18]. Thus, activation of colonic afferents or irritable colon may cause acute sensitization in bladder afferents, at least those traveling in the pelvic nerve, through convergent spinal pathways likely implicating spinal interneurons. In rats with colitis, urinary bladder distension evokes a response of lumbosacral spinal neurons at a lower distension threshold. Urinary bladder distension-responsive neurons are in laminae I–III, V, VI, VII, and X, and no significant difference is found in the regional distribution.

In cats, increasing intravesical or intracolonic pressure alternately suppresses a reflex in the anal or urethral branch of the pudendal nerve induced by electrical stimulation of the contralateral pudendal nerve, suggesting that afferent stimuli that induce micturition and defecation suppress pudendal–pudendal reflexes to the anal and urethral sphinc-

ters, respectively [36]. Thus, mechanisms underlying urinary and distal bowel continence are likely involved in pudendal–pudendal reflexes.

4.1.1.3 Genital Organs

Chronic pain in the perineum, testes, or tip of the penis often overlap with lower urinary tract symptoms such as frequency and urgency of micturition and nocturia, which is analogous to typical symptoms of chronic prostatitis in males [37, 38]. Meanwhile, in females, chronic pain of endometriosis, vaginitis, or vulvovaginitis is also accompanied by lower urinary tract symptoms [39].

The hypogastric nerves play a role as a major source of afferent and efferent innervation of the uterus. Uterine inflammation or experimental endometriosis in rats causes plasma extravasation in the urinary bladder and urinary bladder hypersensitivity, both of which are generated via hypogastric nerve innervation [14].

The perineal skin stimulation by nociceptive pinching normally causes bladder contraction with increases in efferent activity of the pelvic nerve and in periurethral electromyogram activity if bladder pressure is low [29]. Conversely, if the bladder is full, voiding contractions are induced but decreased in frequency and size by the stimulus. The efferent activity of the pelvic nerve is correspondingly decreased, whereas the periurethral electromyogram activity is augmented during and after exposure to the nociceptive stimulus.

Mechanical stimulation of the vagina, vas deferens, or seminal vesicle reduces the frequency and size of bladder contractions, whereby the effect is attributable to a decreased rate of discharge in pelvic efferent fibers if bladder pressure is high [29]. Electrical stimulation of the sensory pudendal nerve or its branches such as dorsal penile/clitoris nerves or stimulation of the intravagina inhibits bladder reflexes and activates sphincter reflexes in humans and animals with or without chronic spinal trauma [30]. In the pudendal-to-pudendal reflex, a pudendal nerve stimulation frequency of <10 Hz produces inhibition, whereas that of 20–40 Hz causes excitation, exhibiting stimulation-frequency-dependency. Correspondingly, electrical stimulation of the perigenital organs induces either an excitatory or an inhibitory spinal reflex to the bladder through activation of a pudendal nerve branch, which also depends on the stimulation frequency.

4.1.2 Efferent Pathways and Reflex Control of the Lower Urinary Tract

4.1.2.1 Parasympathetic Preganglionic Neurons

Dendrites from preganglionic neurons in the lumbosacral parasympathetic nucleus make connections to discrete regions in the spinal cord, those of which are the lateral and dorsal lateral funiculus, lamina I on the lateral edge of the dorsal horn, the dorsal gray commissure, and gray matter and lateral funiculus ventral to the autonomic nucleus (Fig. 4.1) [40, 41]. Relatively unbranched dendrites from the neurons extend for 1.5–2 mm in both gray and white matter. In the cat, a unique feature of sacral preganglionic neurons is characterized by an extensive axon collateral system that makes bilateral projections to a variety of regions in the ventral and dorsal horns, such as the intermediolateral region of the sacral parasympathetic nucleus, the dorsal commissure, and the lateral dorsal horn, and the area around the central canal [42]. These collaterals may be involved in regulating intraspinal integrative actions of preganglionic neurons, such as recurrent inhibition [43, 44] and regulation of sphincter reflexes [45].

4.1.2.2 External Urethral Sphincter Motoneurons

Striated muscle of the external urethral sphincter receives innervation from motoneurons providing pudendal nerves and a subpopulation of the neurons [8, 41]. In cats, the external urethral sphincter motoneurons, which exist in the ventrolateral area of Onuf's nucleus, make dendritic projections to lamina X, the lateral funiculus, the intermediolateral gray matter, and rostro-caudally within the nucleus [46, 47]. Bundles containing the dendrites pass through restricted regions of the spinal cord. Thus, there is a similarity in the dendritic distribution between sphincter motoneurons (i.e., lateral, dorsolateral, and dorsomedial) and sacral preganglionic neurons, implying that the same interneuronal pathways in the spinal cord send synaptic inputs to these two neuronal populations.

4.1.2.3 Pelvic Floor Motoneurons

The lower limit of the true pelvis, referred to as the pelvic diaphragm, is formed by the levator ani and coccygeus (or ischi-coccygeus) muscles. Three muscle groups composed of the iliococcygeus muscle, the puboccygeus muscle, and the puborectalis muscle form the levator ani, the main muscle of the pelvic floor [48]. Studies of human cadavers have shown that the levator ani muscles receive innervation mostly from branches of the pudendal nerve originating in the sacral sphincter motoneurons, that is, the perineal nerve and inferior rectal nerve (in approximately 88% and 35%, respectively), and directed by sacral spinal nerves (S_3 and/or S_4) (in approximately 70%) [49]. The lavator ani muscles are innervated by a variant inferior rectal nerve that is independent of the pudendal nerve (in approximately 40%). The pubococcygeus muscle and the puborectalis muscle both primarily receive innervation from the pudendal nerve branches (in 77%). The iliococcygeus muscle primarily receives innervation from the direct sacral nerves (S_3 and/or S_4) (in approximately 65%). Motoneurons that innervate the levator ani muscle (pelvic floor muscle) are more medially

located in Onuf's nucleus in the ventral horn in contrast to external urethral sphincter motoneurons, which are laterally located [8, 47].

4.1.3 Modulation of the Micturition Reflex by Sacral Interneurons

Retrograde transneuronal labeling by injecting pseudorabies virus, which can cross multiple synapses and thus travel in interneuronal circuitry throughout the central nervous system, into the urinary bladder or urethra of rats has identified in detail brain and spinal interneuronal pathways implicated in the control of lower urinary tract function (Fig. 4.1). Interneurons associated with the urinary bladder or urethra of rats are labeled by the retrograde tracer primarily in laminae I and V, the dorsal commissure, and in regions dorsal and medial to the parasympathetic nucleus (lamina VII) [50–56]. Identification of spinal interneurons in the regions that receive afferent input from the bladder and urethra has also been achieved by firing in response to bladder afferent stimulation [57–59] or by immediate early gene c-fos expression after mechanical or chemical stimulation of the lower urinary tract [60, 61]. Some of these interneurons that receive afferent input from the lower urinary tract make excitatory and inhibitory synaptic connections with the parasympathetic preganglionic neurons [62–65] and participate in segmental spinal reflexes [64]. In contrast, the other interneurons make long connections projecting to supraspinal centers such as the periaqueductal gray, pontine micturition center (Barrington's nucleus), and the hypothalamus and thalamus that participate in the supraspinal control of micturition [58, 61, 66–70].

4.1.4 Reflex Influences on the Striated Muscle of the Urethral Sphincter (Rhabdosphincter) and Pelvic Floor in Humans

Normal lower urinary tract function results from a precise coordination between central and peripheral neural circuits. During urine storage, the bladder remains at low pressure and urethral striated sphincter (rhabdosphincter) activity is gradually increased to maintain continence (continence reflex or guarding reflex) [71]. When voiding occurs, complete relaxation of the urethral rhabdosphincter precedes bladder contraction. The activity of the urethral rhabdosphincter and pelvic floor muscle is controlled by involuntary and voluntary mechanisms. Reflex influences on the urethral rhabdosphincter and pelvic floor muscle activities in humans are described below with regard to 4 aspects of reflexes affecting the lower urinary tract.

4.1.4.1 Vesico-Urethral Reflex during the Urine Storage Phase

As the bladder is gradually distended with increasing urine volume, stretch-sensitive mechanoreceptors in the bladder wall generate afferent signals to the spinal cord and then to the supraspinal micturition centers. At a low volume, the guarding reflex is present with no sensory awareness of the bladder filling state. This phase of the guarding reflex is involuntary in nature. When the sensory threshold for maximum desire to void is reached, the urethral rhabdosphincter activity increases even further as the person actively attempts to hold urine. This phase of the guarding reflex is a conscious and voluntary phenomenon. In humans, the guarding reflex appears to involve supraspinal micturition centers. Siroky and Krane found that the guarding reflex was absent in 84% of the patients with complete spinal cord injury, whereas it was present in 91% of the patients with incomplete spinal cord lesions [72]. According to a previous study using electromyography of the urethral rhabdosphincter, the mean number of action potentials of the urethral rhabdosphincter increased from 8.7 ± 1.3 spikes per second in the empty bladder to 16.9 ± 2.5 spikes per second in 80% of the bladder capacity (indicating a 94% increase) [73]. This reflex increase in urethral rhabdosphincter activity was maintained in male patients who underwent cystoprostatectomy for bladder cancer and orthotopic intestinal neobladder creation (Fig. 4.4).

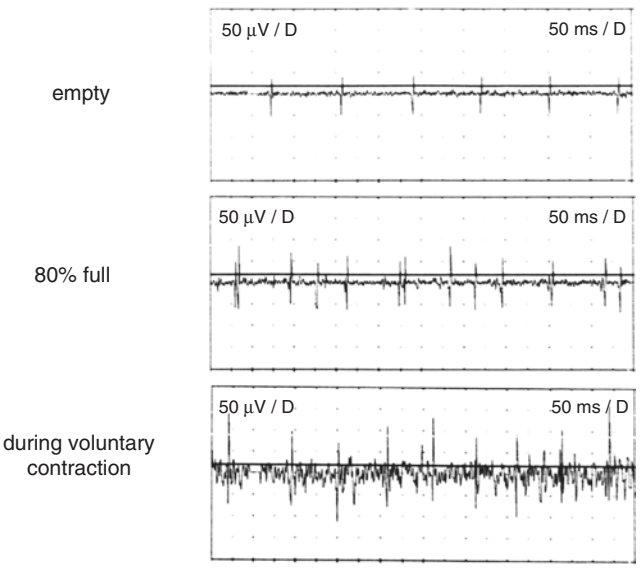

Fig. 4.4 Electromyography of the urethral rhabdosphincter in a male patient who underwent cystoprostatectomy and orthotopic intestinal neobladder creation. Neobladder filling increased the frequency of the action potentials. During voluntary contraction of the urethral rhabdosphincter, the recruitment of action potentials was more intense

4.1.4.2 Active Reflex Contraction during Sudden Abdominal Pressure Increase

A sudden abdominal pressure increase induced by a cough or a sneeze may cause incontinence in women (stress urinary incontinence). Urethral closure mechanisms under stress in women have been the subject of investigations. The existence of a two-component urethral closure mechanism under stress conditions has been proposed: the proximal closure mechanism of the smooth muscle and the distal closure mechanism involving the urethral rhabdosphincter and pelvic floor muscles [74]. The former is important for passive transmission of abdominal pressure. The latter enables exceeding passive increases in bladder pressure by a reflex-mediated fast-acting contraction and augments urethral closure pressure during stress. The fast-acting component of the distal urethral closure mechanism can generate up to twice the amplitude of an intra-abdominal pressure increase during stress. Simultaneous latency measurements during cough in women indicate that the pressure increase in the distal urethra precedes that of the bladder by 240 ± 30 ms [75]. The fast-acting reflex contraction of the urethral rhabdosphincter and pelvic floor muscles during cough composes a part of the guarding reflex.

4.1.4.3 Urethro-Urethral Reflex during the Urine Storage Phase

In experimental studies of cats with the bladder empty, a rapid infusion of saline into the proximal urethra triggers contractions of the urethral rhabdosphincter [76]. This reflex activation of the urethral rhabdosphincter is called the urethro-urethral contraction reflex. When the bladder is sufficiently full to trigger the vesico-urethral relaxation reflex (voiding reflex), the urethro-urethral contraction reflex is never present, indicating that spinal motoneurons (Onuf's nucleus) controlling the activity of the urethral rhabdosphincter are completely inhibited by supraspinal descending neural input. Urethral afferent fibers reach the spinal cord via the pelvic nerve and pudendal nerve [45]. It seems likely that, compared to a simple distension of the bladder or an increase in intravesical pressure, the guarding reflex is actually activated more vigorously by urethral afferent fibers when urine inadvertently enters the bladder neck and the proximal urethra. In this situation, a rapid closure of the distal urethra by contracting the urethral rhabdosphincter is necessary for guarding against urine loss.

4.1.4.4 Somato-Urethral Reflex

Various somatic stimuli, such as tactile and pinch stimulation of the perineum, trigger contraction of the urethral rhabdosphincter [77, 78]. Because the somato-urethral contraction reflex is a spinal reflex, it is maintained after spinal cord injury. Mechanical stimulation to the perineum also triggers contraction of pelvic floor muscles (e.g., bulbocavernosus reflex and anal reflex). These reflexes can be used to test the integrity of spinal reflex pathways.

4.1.5 Modulation of Micturition by Descending Pathways

Retrograde tracing by pseudorabies virus injection has identified that a number of neuronal populations in the rat brain involved in the control of the bladder, urethra, and external urethral sphincter are present in the periaqueductal gray, pontine micturition center (Barrington's nucleus), locus coeruleus that contains noradrenergic neurons, A5 noradrenergic cell group, and medullary raphe nuclei that contain serotonergic neurons [50, 51, 55]. Efferent neurons and interneurons in the spinal cord and a cluster of neurons that extends from the pontine micturition center ventrolaterally to the pontine reticular formation, many of which are associated with the innervation of the urinary bladder or the external urethral sphincter, have been identified in cats [70, 79–83].

Another anterograde tracer injected into the paraventricular nucleus of the hypothalamus in cats identified terminals in the parasympathetic nucleus and the sphincter motor nucleus in the sacral spinal cord (Fig. 4.1) [70]. Injection of the tracer into the pontine micturition center labeled axonal projections to the sacral parasympathetic nucleus, the lateral edge of the dorsal horn and the dorsal commissure, areas that contain dendrites of preganglionic neurons, sphincter motoneurons, and afferent inputs from the bladder [70]. Additionally, neurons in the ventrolateral pons of cats, which has been identified as the pontine urine storage center, send relatively selective projections to the sphincter motor nucleus [70, 80]. Thus, descending projections from the pons terminate at the optimal spinal sites to regulate reflex mechanisms of the lower urinary tract function.

4.1.5.1 Descending Aminergic Pathways

Adrenergic

The thoracolumbar sympathetic nucleus and the lumbosacral parasympathetic nucleus in the spinal cord receive inputs from neurons containing noradrenaline in the brainstem [84, 85]. The majority of the inputs are from neurons in the locus coeruleus that modulate excitatory and inhibitory actions on the lower urinary tract activity via adrenoceptors.

In anesthetized cats, electrical stimulation of the locus coeruleus causes bladder contraction, which is blocked by the intrathecal administration of prazosin, an α_1-adrenoceptor antagonist [86]. Lesions in adrenergic neurons induced via the microinjection of 6-hydroxydopamine, a selective catecholaminergic neurotoxin, into the locus coeruleus produce bladder underactivity, and the activity is partially reversed by phenylephrine, an α_1-adrenoceptor agonist. These results suggest that adrenergic projections from the brainstem to the sacral parasympathetic nucleus via α_1-adrenoceptors are important in inducing bladder contractions. However,

although the bulbospinal noradrenergic excitatory mechanism controlling voiding function has been demonstrated in cats under anesthetized conditions, studies performed in conscious cats have not confirmed these findings [87].

In both conscious and anesthetized rats, intrathecal injection of doxazosin, an α_1-adrenoceptor antagonist, increases the frequency of isovolumetric bladder contractions and decreases the amplitude of the reflex bladder contractions, indicating that afferent and efferent limbs in the reflex micturition circuit receive inhibitory and excitatory inputs, respectively, from noradrenergic projections in the spinal cord [88]. The former is supported by the finding that the intrathecal injection of phenylephrine increases the interval between two consecutive isovolumetric bladder contractions [88]. These results suggest that the spinal noradrenergic mechanism in rats has regulatory roles in producing tonic inhibition on the processing of afferent input from the bladder and in mediating the parasympathetic excitatory outflow to the bladder. However, the effect of α_1-adrenergic modulation on the bladder afferents remains controversial [89].

In rats, the α_1-adrenoceptor subtype primarily involved in spinal parasympathetic excitatory outflow has been shown to be α_{1A} [90]. With respect to α_1-adrenoceptor subtypes in the rat lumbospinal cord, a radioligand analysis has shown that the expression of α_{1A} and α_{1B} receptors is 70% and 30%, respectively, and the α_{1D} receptor is only sparsely present [91]. In contrast, a study with *in situ* hybridization probes to examine the mRNA expression of α_1-adrenoceptor subtypes in the human spinal cord has revealed that α_{1d} is the most abundant, with α_{1a} and α_{1b} being much less abundant (Table 4.1) [92]. Thus, the expression of the α_1-adrenoceptor subtypes varies in different species, and the involvement of each α_1-adrenoceptor subtype in the human spinal cord in controlling lower urinary tract function is assumed to be different from that in rats.

Table 4.1 Analysis of the mRNA distributions of the α_1-AR and α_2-AR subtypes in human spinal cord using *in situ* hybridization

	α_1	α_2
Sympathetic (Mid-thoracic/Lumbar)	1a—3+/3+ 1b—4+/4+ 1d—8+/6+	2a—2+/5+ 2b—4+/7+ 2c—0/2+
Dorsal horn (Sacral sensory input)	1a—0 1b—0 1d—0	2a—3+ 2b—8+ 2c—0
Parasympathetic (Sacral intermediate cell column)	1a—3+ 1b—3+ 1d—8+	2a—3+ 2b—6+ 2c—0
Ventral horn (Sacral motor/Onuf's nucleus)	1a—4+ 1b—3+ 1d—10+	2a—3+ 2b—10+ 2c—0

Valid comparisons of data are made within tissues and subtypes and between those. Note: signal ranges from 0 (background) to 10+ (maximal signal). *AR* adrenoceptor. α_1-AR mRNA signal is ≈30% of that found for α_2-AR [92, 93]

The function of α_2-adrenoceptors in the spinal cord is vague, as studies in rats have shown both facilitatory and inhibitory roles of α_2-adrenoceptors in the control of micturition. The intrathecal administration of atipamezole, an α_2-adrenoceptor antagonist, increased voiding pressure in conscious rats, thereby suggesting the existence of a tonic inhibitory adrenoceptor control [94]. However, yohimbine, an α_2-adrenoceptor antagonist, inhibited micturition in anesthetized rats, which is indicative of excitatory involvement of α_2-adrenoceptor [95]. In conscious cats with spinal cord transection, clonidine, an α_2-adrenoceptor agonist, increased intravesical pressure and facilitated micturition [96]. Conversely, in patients with paraplegia, intrathecal administration of clonidine suppressed bladder hyperreflexia [97]. In the human spinal cord, mRNA expression of α_{2b} is more predominant in spinal regions associated with lower urinary tract function compared with that of α_{2a}, and α_{2c} is not present or is only barely expressed (Table 4.1) [93].

Spinal noradrenergic mechanisms also modulate the bladder-to-sympathetic reflex pathway [98]. In chloralose-anesthetized cats, an α_1-adrenoceptor antagonist or an α_2-adrenoceptor agonist suppresses spontaneous firing or the reflex discharge evoked on the hypogastric (sympathetic) nerve in response to stimulation of pelvic nerve afferents [99]. The result of the α_1-adrenoceptor antagonist suggests that a bulbospinal noradrenergic projection provides a tonic α_1-adrenergic excitation in the control of the bladder-sympathetic reflex in the spinal cord. Although α_2-adrenoceptor inhibitory systems are inactive under normal conditions, these can be upregulated by a noradrenaline reuptake inhibitor that elevates endogenous noradrenaline levels [100]. Thus, both α_1-excitatory and α_2-inhibitory mechanisms control the lumbar sympathetic outflow to the bladder.

Serotonergic

Axons from serotonergic neurons in the raphe nucleus of the caudal brainstem project onto the lumbosacral spinal cord to modulate the processing of afferent input from the urinary bladder (in the dorsal horn), the parasympathetic efferent outflow to the bladder (in the autonomic nuclei), and somatic efferent outflow to the striated muscle of the urethral sphincter (in the sphincter motor nuclei) [84, 101].

Activation of raphe neurons or spinal 5-hydroxytryptamine (5-HT) receptors in cats suppresses reflex bladder activity and firing of the sacral efferent limbs to the bladder [102–106] and inhibits firing of spinal dorsal horn neurons induced by pelvic nerve afferent stimulation [107]. Extracellular recording of neuronal activity in the raphe nucleus during the rhythmic bladder contraction cycle in cats has shown that approximately 50% of neurons are the tonic storage type that exhibits augmented firing in intervals between reflex bladder contractions [106].

In conscious cats, an intrathecal injection of methysergide, a nonselective 5-HT_1/5-HT_2/5-HT_7 receptor antagonist, or zatosetron, a 5-HT_3 antagonist, decreases the volume threshold for inducing voiding [108], suggesting that descending serotonergic pathways produce a tonic inhibition on the afferent limb of the micturition reflex via the 5-HT_3 receptor and any of the 5-HT_1/5-HT_2/5-HT_7 receptor subtypes(mostlikely5-HT_2)(Fig.4.5).m-Chlorophenylpiperazine (mCPP), a 5-$HT_{2C/2B}$ receptor agonist, systemically administered to rats suppresses efferent nerve activity of the bladder and reflex bladder contractions [109], and the effects are inhibited by mesulergine, a 5-$HT_{2C/2A}$ receptor antagonist [109, 110], suggesting that the 5-HT_2 receptor (most likely the 5-HT_{2C} subtype) is involved in the inhibition.

Systemic injection of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), a 5-HT_{1A} receptor agonist, increases bladder capacity in chloralose-anesthetized cats with acetic acid irritation-induced bladder hyperreflexia but produces only a small change in activity of the bladder while not having the irritation [111]. Additionally, 8-OH-DPAT suppresses reflex bladder contractions in chloralose-anesthetized or awake cats with chronic spinal cord injury [112]. WAY100635, a 5-HT_{1A} receptor antagonist, which alone has no effect, blocks the effect of 8-OHDPAT [112]. Thus, 8-OH-DPAT exerts actions in the spinal cord to suppress the reflex bladder contractions elicited by C-fiber bladder afferent pathways and produces much less effect on the spinobulbospinal reflex induced by Aδ-afferents (Fig. 4.5) [112].

In contrast, intrathecal injection of 8-OH-DPAT facilitates bladder motility in both normal rats and rats with spinal lesion but does not produce such an effect in rats in which the C-fiber bladder afferents have been desensitized by capsaicin treatment at birth [113]. Additionally, systemically or intracerebroventricularly administered WAY100635, which augments the firing rate of raphe neurons by blocking 5-HT_{1A} inhibitory autoreceptors, suppresses reflex bladder activity in rats (Fig. 4.5) [114, 115]. The inhibition can be antagonized by pretreatment with mesulergine, suggesting that 5-$HT_{2C/2A}$ receptors participate in the raphe-to-spinal descending inhibitory pathways. The effects of intrathecal injection of WAY100635 on the ascending and descending limbs of the micturition reflex pathway have been investigated in anesthetized rats [116]. WAY100635 depresses bladder contractions induced by electrical stimulation of the pontine micturition center but does not change the evoked field potentials in regions where the periaqueductal gray is present during electrical stimulation of afferent axons in the pelvic nerve, suggesting that the 5-HT_{1A} receptor in the bulbospinal descending 5-HT mechanism is involved in the excitatory control of parasympathetic preganglionic outflow to the bladder but does not participate in processing afferent input from the bladder.

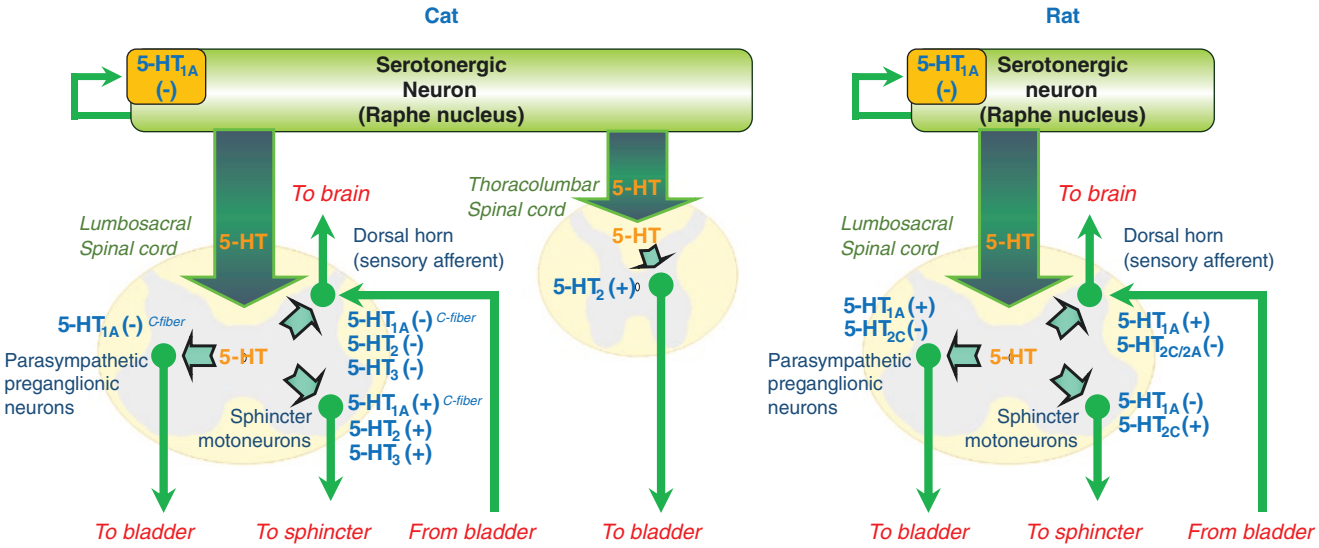

Fig. 4.5 Central serotonergic mechanisms involved in the control of lower urinary tract function in cats (left) and rats (right). Blockade of 5-HT_{1A} inhibitory autoreceptors in brainstem raphe neurons increases firing of raphe neurons and in turn facilitates 5-HT release in the spinal cord. The descending projections from the brainstem raphe neurons to the spinal cord regulate processing of afferent input from the urinary bladder, parasympathetic and sympathetic efferent outflows to the bladder, and somatic efferent outflow to striated muscle of the external urethral sphincter. Indication of excitatory (+) or inhibitory (−) for each 5-HT subtype has been determined based on the results of pharmacological experiments. Superscript "*C-fiber*" indicates a contribution of 5-HT_{1A} under pathological conditions such as lower urinary tract irritation. Because 5-HT_1 and 5-HT_2 generally exert inhibitory and excitatory modulations, respectively, there is likely to be inhibitory interneurons at sites indicating 5-HT_{1A} (+) or 5-HT_{2C} (−)

Dopaminergic

The dopaminergic mechanism in the central nervous system exerts an inhibitory effect via D_1-like (D_1 or D_5) receptors and a facilitatory effect via D_2-like (D_2, D_3, or D_4) receptors on the micturition reflex [117–124]. Stimulation of D_1-like receptors with SKF38393, a selective D_1/D_5 receptor partial agonist, or pergolide, a dopamine receptor agonist, suppresses bladder hyperreflexia induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys [119]. In contrast, activation of central D_2-like dopaminergic receptors with quinpirole, a selective D_2 and D_3 receptor agonist, or bromocriptine, a dopamine agonist, enhances the micturition reflex in rats, cats, and monkeys [118–121, 123]. Facilitation of the micturition reflex mediated by D_2-like receptors is likely to involve actions on the brainstem and the spinal cord because microinjection of dopamine to the pontine micturition center reduces bladder capacity and facilitates the reflex micturition frequency in cats [104], and intrathecal injection of quinpirole causes bladder hyperreflexia in healthy rats and rats with 6-hydroxydopamine-induced lesions in nigrostriatal pathways [123].

4.1.5.2 Spinal Opioid Modulation

Epidural opioids are generally used to relieve acute and chronic pain. However, epidural morphine, a selective μ-opioid receptor agonist, often causes a distressing and troublesome complication such as urinary retention, markedly relaxing the detrusor shortly after its administration [125]. The underlying mechanism for the voiding dysfunction caused by epidural morphine has not been fully elucidated. A possible explanation is that epidural morphine exerts an inhibitory effect at the brainstem or spinal cord, where essential micturition centers exist and where opioid receptors are distributed. Morphine given into the epidural space travels in cerebrospinal fluid not only to the spinal cord but also rostrally to supraspinal structures [126]. Additionally, injection of naloxone, a nonselective opioid receptor antagonist, produces a significant increase in intravesical pressure during cystometry in humans with detrusor overactivity [127]. Naloxone further deteriorates bladder instability during cystometry in patients with incomplete suprasacral spinal cord injury and decreases the bladder volume threshold for inducing micturition by approximately one-third [128]. These findings suggest that endogenous opioidergic mechanisms have an essential role in regulating urine storage and voiding.

There are wide distributions of opioid receptors in the brain, spinal cord, peripheral sensory and autonomic nerves. These receptors in the brainstem, parasympathetic nuclei in the sacral spinal cord, urethral sphincter motor nucleus (i.e., Onuf's nucleus), and intramural plexus of the bladder wall are involved in controlling lower urinary tract function [129–138]. Four subtypes of the opioid receptor have been well characterized, which are δ, κ, μ, and nociceptin receptors.

In cats, intracerebroventricular administration of [D-Ser^2,Leu^5,Thr^6]-Enkephalin (DSLET), a selective δ (putative δ2) opioid receptor agonist, or morphine produces inhibitory effects on reflex bladder contractions, and the effects are blocked by naloxone, thereby suggesting that both μ- and δ-opioid receptors in the brain mediate inhibitory effects on bladder activity [134]. Naloxone administered intracerebroventricularly alone or injected directly into the pontine micturition center enhances the micturition reflex [138–141].

Administration of naloxone to the sacral spinal cord of cats increases the duration and amplitude of bladder contractions and produces sustained vesical efferent firing but does not change bladder capacity [134]. When given intrathecally, DSLET suppresses bladder activity, but morphine produces no effect on either bladder amplitude or contraction frequency. These results suggest that the opioidergic mechanism via δ-opioid receptors, but not μ-opioid receptors, sends inhibitory synapses to the parasympathetic preganglionic neurons to modulate bladder contraction amplitude, presumably in the interneurons of the spinal cord.

In rats, μ- and δ-opioid receptors, but not κ receptors, in the brain and the spinal cord are implicated in the inhibition of bladder reflexes [142, 143]. Activation of the spinal opioid inhibitory system by tachykinins via NK3 receptors [144] and by endothelins via endothelin A receptors [145] appears to also inhibit the micturition reflex.

Pudendal or tibial nerve neuromodulation for treating overactive bladder symptoms involves opioidergic mechanisms as naloxone reverses the increasing effect of pudendal or tibial nerve stimulation on bladder capacity under normal conditions or intravesical acid irritation in cats [146–149]. However, because of the systemic injection of naloxone, the site of action for opioid receptor activation during neuromodulation can be other than the spinal cord. With respect to S_1-S_2 sacral neuromodulation-mediated suppression of bladder hyperreflexia caused by intravesical irritation, a spinal involved $GABA_A$ mechanism exerts its inhibitory effect via spinal opioid receptors.

In chronic spinal cord injured cats, dogs, and rats presenting automatic urination, systemic or intrathecal injection of naloxone causes large rhythmic bladder contractions and spontaneous voiding and enhances somato-bladder reflexes [139, 150–152], indicating that the spinal pathways controlling urination in paraplegic animals are under a tonic opioidergic inhibition. The phenomenon is in contrast to healthy animals, whereby intrathecally given naloxone produces no change in bladder capacity. Thus, in normal animals, opioidergic mechanisms to control bladder capacity are present in the brain, whereas in paraplegic animals, they are shifted in the spinal cord.

4.1.6 Selective Pharmacological Modulation of Urethral Sphincter Activity

4.1.6.1 Monoaminergic Mechanisms

Adrenergic

Neurons containing noradrenaline in the brainstem project to the sphincter motor nucleus (i.e., Onuf's nucleus) [99, 153–155] and thoracolumbar sympathetic nucleus [99, 156], as well as the lumbosacral parasympathetic nucleus [86, 157, 158], and the spinal noradrenergic mechanisms modulate urethral function. Prazosin, an α_1-adrenoceptor antagonist, suppresses sympathetic and somatic pathways to the lower urinary tract in cats [99, 153]. Clonidine, an α_2-adrenoceptor agonist, inhibits striated sphincter reflexes in cats [96] and humans [97]. These findings suggest that α_1-adrenoceptors and α_2-adrenoceptors exert tonic excitatory and inhibitory modulations of urethral function, respectively (Fig. 4.6).

The continence-maintaining mechanism partially involves the activation of urethral sphincter motoneurons by stimulating bladder (pelvic nerve) or urethral/perineal (pudendal nerve) afferents. Prazosin, but not idazoxan, an α_2-adrenoceptor antagonist, suppresses these reflexes presented as efferent discharges on the pudendal nerve in chloralose-anesthetized cats [99, 100, 153]. Whole-cell patch clamp experiments in rat neonatal spinal cord slices show that noradrenaline depolarizes urethral sphincter motoneurons and evokes action potentials, those of which are blocked by prazosin [155]. The results suggest that there is a direct facilitatory mechanism that increases the excitability of urethral sphincter motoneurons by noradrenaline via α_1-adrenoceptors. In contrast, clonidine suppresses the pudendal nerve reflex in anesthetized cats [159]. Tomoxetine, a noradrenalin reuptake inhibitor, alone causes a small inhibition and produces slightly greater suppression when given after prazosin [99]. It greatly enhances the reflex, however, when administered after idazoxan. These results suggest that α_1-adrenoceptor and α_2-adrenoceptor mediate a tonic facilitation and inhibit the control of sphincter function, respectively, and that the α_2-adrenoceptor-dependent inhibition

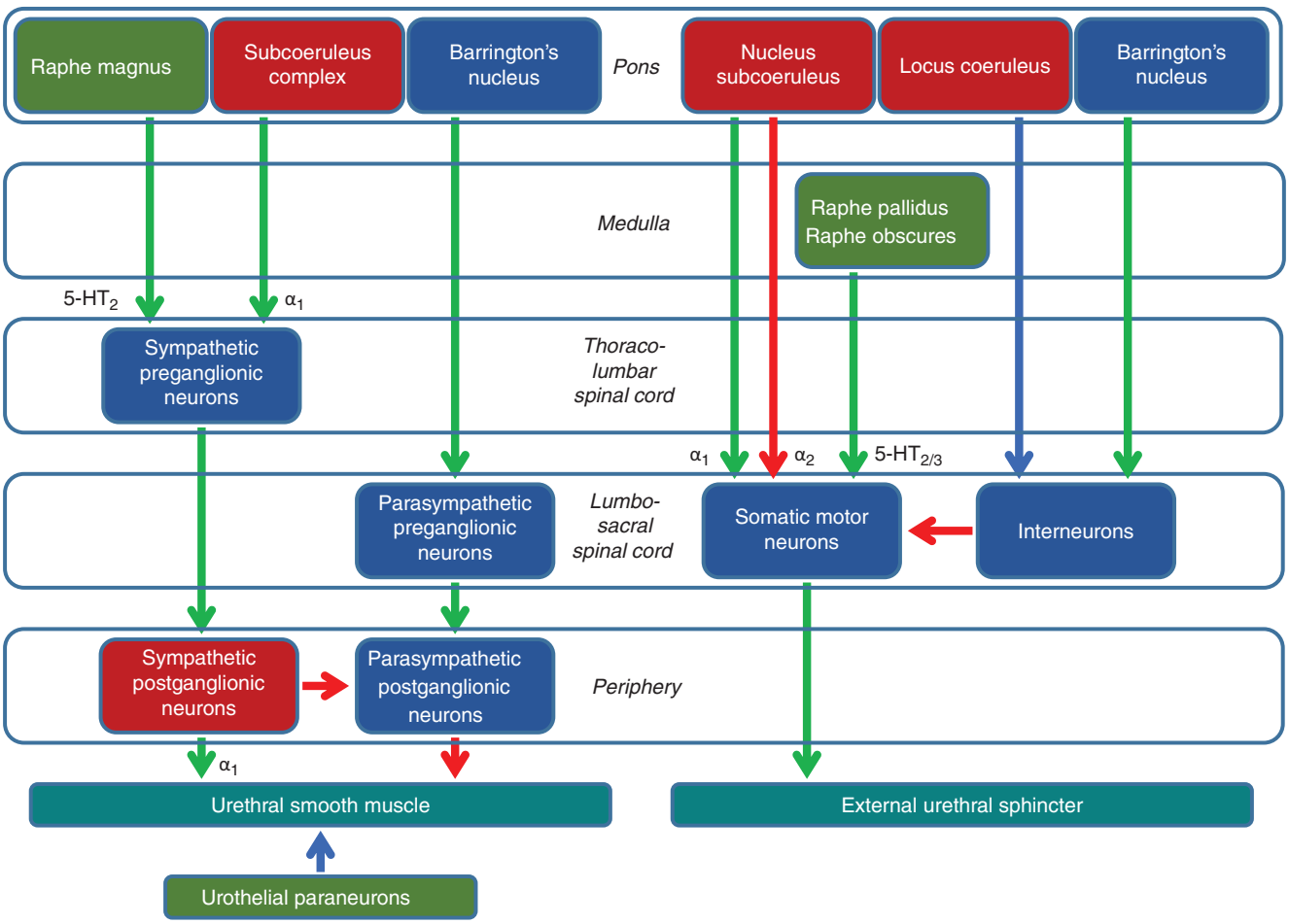

Fig. 4.6 Hypothetical descending monoaminergic projections in the control of urethral smooth muscle (left) and the external urethral sphincter (right). Green and red indicate serotonergic and noradrenergic sources, respectively. Red, green, and blue arrows indicate inhibition, excitation, and unknown, respectively

plays a dominant role in the adrenergic modulation of the pudendal nerve reflex [154].

The α_1- and α_2-adrenoceptor-modulated excitatory and inhibitory mechanisms, respectively, contribute to prevention of stress urinary incontinence by enhancing the urethral continence reflex (Fig. 4.6) because nisoxetine, a noradrenaline reuptake inhibitor, or duloxetine, a noradrenaline/serotonin reuptake inhibitor, induces α_1-adrenoceptor activation in the lumbosacral spinal cord [160, 161] and enhances reflex contractions of the external urethral sphincter during sneezing, and an α_2-adrenoceptor antagonist, yohimbine or idazoxan, enhances urethral sphincter contraction induced by duloxetine during sneezing or abdominal compression in rats [162, 163].

The relationships between external urethral sphincter activity and urinary continence during increased abdominal pressure have been demonstrated in rats. In the dorsal horn of the spinal cord and the presynaptic α_2-adrenoceptor of the sympathetic preganglionic neurons, α_2-adrenoceptors modulate the release of glutamate (excitatory amino acid) from the synaptic terminals (Fig. 4.7) [162]. In experiments examining the pelvic-to-pudendal spinal reflex in response to a passive increase in abdominal pressure in rats with acute spinal cord transection, medetomidine, an α_2-adrenoceptor agonist, reduces external urethral sphincter activity in a dose-dependent manner. Idazoxan increases external urethral sphincter activity by 64%, which was abolished by MK-801, an N-methyl-D-aspartic acid (NMDA) glutamatergic receptor antagonist. Conversely, idazoxan does not block the inhibitory effect of MK-801. Idazoxan enhances the effect of noradrenaline/serotonin reuptake inhibitor on external urethral sphincter activity by 120%. In the pelvic-pudendal reflex that occurs in response to an increase in abdominal pressure facilitating urinary continence, glutamate is the major excitatory neurotransmitter. Additionally, in the spinal cord, α_2-adrenergic presynaptic stimulation suppresses glutamate release from the primary afferent in the dorsal horn and from the presynapse to Onuf's nucleus in the ventral horn. Thus, an α_2-adrenoceptor antagonist enhances the effect of serotonin-noradrenaline reuptake inhibitor on the external urethral sphincter to maintain urinary continence.

Serotonergic

The urethral sphincter motor nucleus (i.e., Onuf's nucleus) and the sympathetic autonomic nucleus receive descending projections from the brainstem containing serotonin (i.e., raphe nucleus) (Figs. 4.6 and 4.7) [108, 154, 164]. An autoradiography study revealed the existence of 5-HT_{1A} receptors and 5-HT_2 receptors in Onuf's nucleus of rats [165]. In cats, pharmacological experiments showed that spinal serotonergic activity via 5-HT_2 and 5-HT_3 receptors plays an excitatory role in the pudendal nerve reflex [108, 166], thereby facilitating urine storage by enhancing sphincter reflexes.

In cats, large doses of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), a nonselective 5-HT agonist that activates 5-HT_{1A} and 5-HT_2 receptors, enhance sympathetic firing of the hypogastric nerve, increase urethral sphincter electromyogram activity, and decrease the supraspinal micturition reflex [167]. In contrast, small doses of 5-MeO-DMT suppress sympathetic and sphincter activity by inhibiting firing of raphe neurons via action on 5-HT_{1A} autoreceptors in the raphe nuclei. The former facilitatory effects are most likely due to a direct excitatory effect via 5-HT_2 receptors, whereas the latter inhibitory effects are attributable to suppression of tonic raphe excitatory input to sympathetic preganglionic neurons and sphincter motoneurons.

In rats, activation of $5HT_{2C}$ receptors at the spinal level facilitates the urethral closure reflex elicited by urethral striated muscle contraction in response to pudendal nerve mediation during sneezing, whereas activation of $5HT_{1A}$ receptors suppresses it because intrathecal injection of 8-OH-DPAT, a $5HT_{1A}$ agonist, reduces contraction responses of the urethra during sneezing, and mCPP, a $5HT_2$ agonist, enhances the responses [168]. The effects of 8-OH-DPAT and mCPP were inhibited by intrathecal administration of WAY100635, a selective $5HT_{1A}$ antagonist, and RS-102221, a selective $5HT_{2C}$ antagonist, respectively. In contrast, 8-OH-DPAT produced a facilitatory effect on external urethral sphincter activity during bladder filling in chloralose-anesthetized cats subjected to bladder irritation with acetic acid, which was reversed by WAY100635 [111]. Thus, involvement of 5-HT_{1A} receptors in lower urinary tract function appears to be different in cats and rats.

4.1.6.2 Opioid Mechanisms

The urethral sphincter motor nucleus in cats is largely innervated by terminals containing opioid peptide immunoreactivity [133, 135]. This innervation differentiates the urethral sphincter motor nucleus from other lumbosacral motor nuclei that exhibit a paucity of opioid-containing terminals.

In cats, intrathecal injection of ethylketocyclazocine, a κ-opioid receptor agonist, dose-dependently produces an inhibition of the urethral sphincter reflex, which is reversed by naloxone but does not affect bladder activity [46]. Systemic administration of naloxone, however, has no effect on physiological inhibition of the urethral sphincter reflex that is present during bladder contractions. Additionally, intrathecal injection of DSLET, a δ-opioid receptor agonist, or morphine, a μ-opioid receptor agonist, produces no effect on the urethral sphincter reflex [46]. These results suggest that activation of the spinal κ-opioid receptor but neither the δ-opioid receptor nor the μ-opioid receptor selectively suppresses reflex mechanisms that modulate the function of the external urethral sphincter. The κ-opioid receptor also participates in inhibition of external urethral sphincter activity in rats [169].

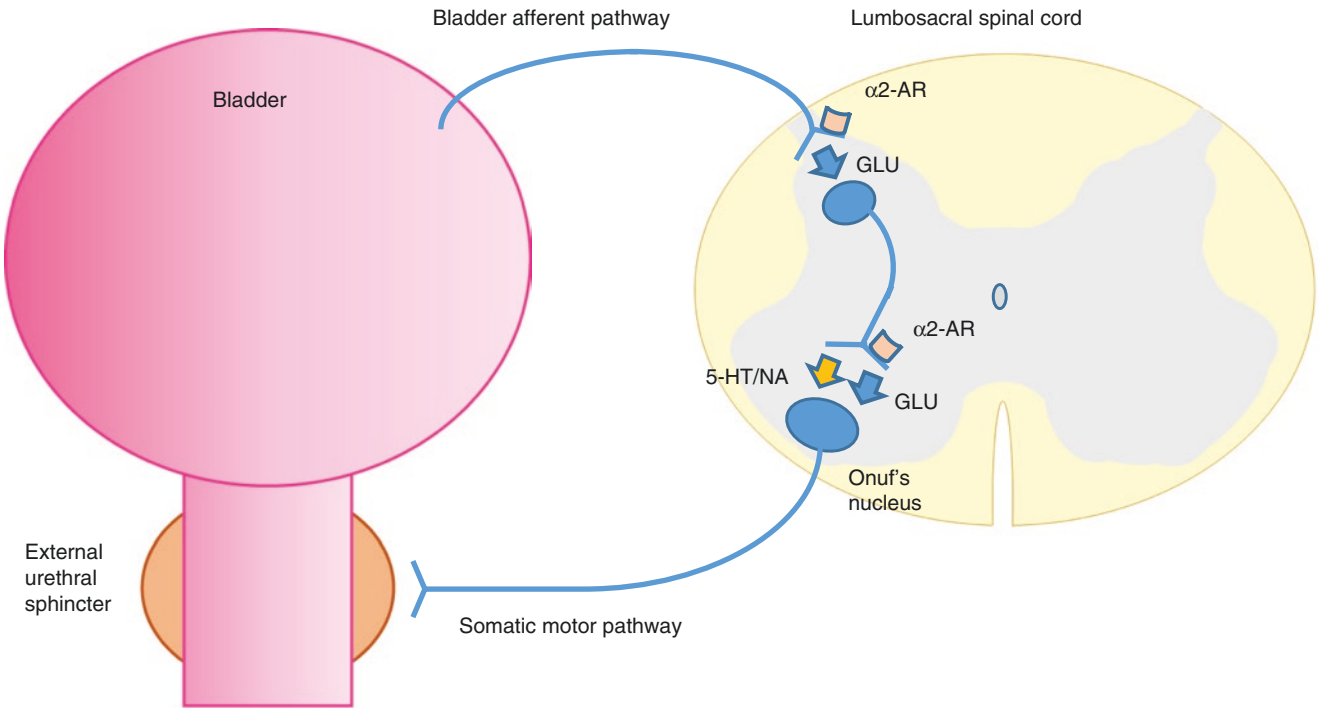

Fig. 4.7 Schematic showing hypothetical adrenergic and glutamatergic mechanisms in the control of the external urethral sphincter continence reflex in response to compression of the abdomen. Activation of the α_2-adrenoceptor depresses the external urethral sphincter activity, presumably via α_2-adrenoceptor-mediated presynaptic inhibition of glutamate release. An α_2-adrenoceptor antagonist, which suppresses α_2-adrenoceptor activation caused by increased noradrenaline, can enhance the effects of serotonin/noradrenaline reuptake inhibitors. *GLU* glutamate; *α₂-AR* α_2-adrenoceptor; *5-HT* 5-hydroxytryptamine (serotonin); *NA* noradrenaline

4.1.7 Testing of LUT Reflex Pathways in Humans

The storage and voiding phases of the normal micturition reflex are coordinated by reciprocal activities of the bladder and urethra. Reflex activity of the bladder and urethra in humans can be tested by urodynamic studies. The integrity of the lower urinary tract reflex pathways, specifically the sacral reflex arc, can be tested using various neurophysiological methods.

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Central Pathways That Control the Urinary Bladder

5

Bertil Blok

5.1 Introduction

In order to understand the role of the brain in the control of the urinary bladder and its sphincter, it is important to make a distinction between (1) Areas and pathways which are intrinsic part of the micturition and continence reflex, and (2) Areas and pathways which modulate these micturition and continence areas. Most of the clinical therapies aimed at alleviating functional bladder disorders are not specifically targeted on the central reflex areas, like the pontine micturition center (PMC), but influence cortical and subcortical brain areas which modulate the micturition reflex components. Examples of such therapies are pelvic floor physiotherapy, biofeedback, medication which pass the blood-brain barrier, transcutaneous electrical nerve stimulation, posterior tibial nerve stimulation and sacral neuromodulation. At this moment, there are probably no effective behavioral, electrical or chemical treatment which work directly and specifically on the central components of the micturition reflex.

5.2 Specific and Non-specific Ascending Supraspinal Sensory Pathways

As discussed in detail in the previous chapters, the afferent nerves of the urinary bladder convey sensory information via the pelvic and hypogastric nerves to the lumbosacral spinal cord. The afferent information from the bladder neck and urethra is conveyed via the pudendal and hypogastric nerves to the spinal cord. The lower urinary tract afferents terminate on interneurons in the lateral aspect of the dorsal horn and in the intermediate zone of the lumbar and sacral spinal cord [1, 2]. Most of these interneurons make intraspinal connections, but some spinal interneurons send ascending projections supraspinally to specific areas in the pons and midbrain that are involved in the micturition reflex (Fig. 5.1). These interneurons are involved in the relay of bladder filling sensation. The circuitry through which information from the urinary bladder is conveyed to the brain varies somewhat depending on the species in which the anatomy was characterized. Other interneurons relay information from the lower urinary tract to forebrain structures, including the thalamus and the hypothalamus [3]. The spinothalamic and spinohypothalamic tracts are though not to play a specific role in the basic micturition reflex, but are involved in the conscious awareness of bladder filling. The sensory cortex is via the spinothalamic tract constantly informed about the filling state of the urinary bladder. In overactive bladder patients there is too much awareness of bladder filling, which can be suppressed by therapies, like pelvic floor physiotherapy or sacral neuromodulation.

5.2.1 Pontine Micturition Center (PMC) and Its Descending Spinal Motor Pathway

In 1925 Barrington was the first to describe a pontine control center for micturition in the cat on the basis of bilateral lesion studies [4]. This region was localized in the dorsal pons and is now termed pontine micturition center (PMC) or Barrington's nucleus. Later studies using more discrete lesions that abolished micturition and caused urinary retention in cats and rats [5, 6]. Lesions in humans as a result of stroke or multiple sclerosis in an analogous region similarly result in urinary retention in man [7, 8].

The PMC is located in the dorsal pons ventromedial to the rostral pole of the locus coeruleus (LC) in the rat, but intermingled with neurons the LC in the cat [9]. In humans, comparable regions in the pons have been described recently in the dorsal part of the pontine tegmentum, including the possible PMC [10].

The descending axons from the PMC have been described to project to the sacral cord [11]. These axons have excitatory terminal boutons in the intermediolateral cell column on

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_5

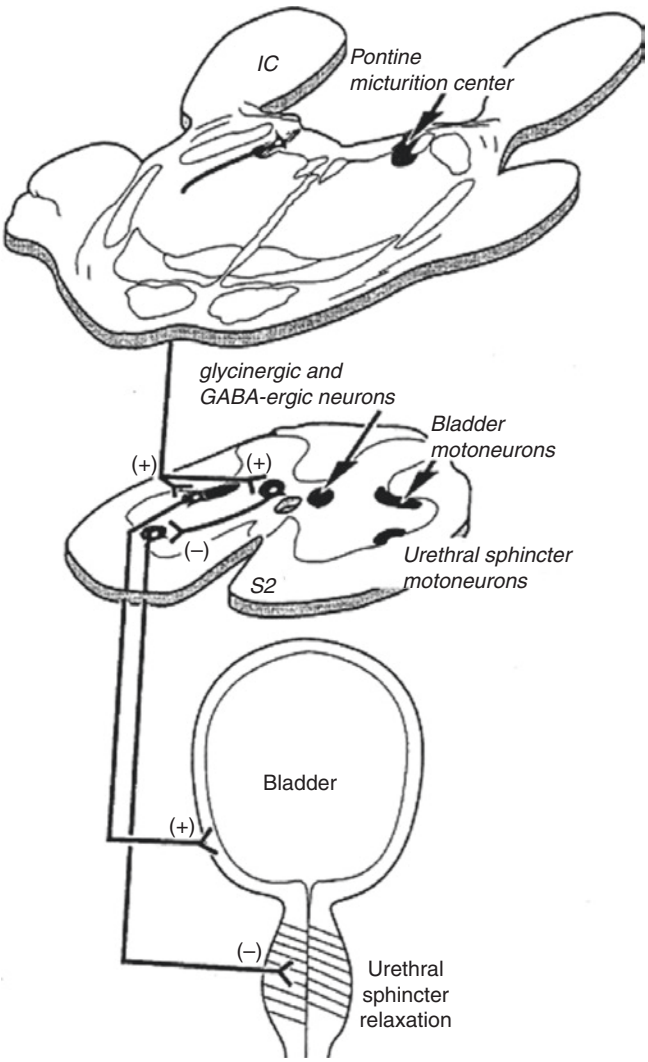

Fig. 5.1 Descending micturition pathway from the pontine micturition center to the sacral cord

parasympathetic preganglionic motoneurons innervating postganglionic neurons in the bladder wall [12]. Both electrical and chemical activation of the PMC in rats and cats initiates bladder contractions and relaxes the urethral sphincter mimicking normal micturition [13–15].

There micturition reflex cycle consists of three phases controlled by separate central pathways: (1) pre-micturition phase during realization of a safe environment; (2) relaxation phase during relaxation of the external urethral sphincter; and (3) contraction phase during contraction of the detrusor muscle. Normal micturition does not take place without the onset of one of these phases. Phase 1—pre-micturition phase—is controlled via a forebrain (hypothalamic) pathway to the PAG and PMC which initiates micturition; phase 2—urethral relaxation phase—is controlled via an excitatory descending PMC pathway to inhibitory sacral interneurons; and phase 3—the contraction phase—via the excitatory descending PMC pathway to sacral preganglionic bladder motoneurons.

The urethral relaxation pathway from the PMC to the sacral spinal cord does not terminate directly on the motoneurons of the external urethral sphincter in the Onuf's nucleus (Fig. 5.1). It terminates in the intermediomedial cell column, also called dorsal gray commissure or lamina X, and makes contact with inhibitory interneurons containing GABA and glycine [16, 17]. These inhibitory interneurons, in turn, project specifically to the motoneurons of the striated external urethral sphincter [18]. Stimulation of the sacral intermediomedial cell column of the cat results in a strong relaxation of the external urethral sphincter, mimicking the relaxation of the sphincter during micturition [19].

Together, the anatomical and physiological findings described above point to the PMC as being the command center or the switch during micturition for both the relaxation phase involving the external urethral sphincter and the contraction phase involving the smooth detrusor muscle of the urinary bladder.

5.2.2 Pontine Continence Center (PCC) and Its Descending Spinal Motor Pathway

The bladder's function of urine storage requires detrusor relaxation accompanied by urethral sphincter contraction. Studies in the cat identified a pontine continence center (PCC) also termed the L(ateral)-region that is distinct from and lying ventrolateral to the PMC or M(edial)-region [14]. Neurons in this region project specifically to Onuf's nucleus in the sacral cord, which contains the external urethral sphincter motoneurons. Stimulation of this region stops micturition, excites the pelvic floor musculature and contracts the urethral sphincter. Conversely, bilateral lesions of the PCC cause incontinence, excessive detrusor activity, an inability to store urine and relaxation of the urethral sphincter [14]. However, there is no anatomical evidence for connections between the PMC and the PCC and it has been suggested that the PMC and PCC function independently [20]. Notably, the PCC has also been characterized by PET scanning in humans who try to start micturition [21, 22] or orgasm [23], but fail to do so.

5.2.3 Periaqueductal Gray (PAG)

The mesencephalic periaqueductal gray (PAG) is main area in the caudal brainstem in the cat and probably also in humans which receives bladder information [24]. The PAG is a midbrain area known for its role in pain modulation [25]. In recent years it has become clear that this dense neuronal matter around the aqueduct of Sylvius is essential for many vital basic functions, like respiration, aggression, mating, defecation and micturition. The forebrain controls the PAG and the PMC like a

switch. Complex behavior like micturition can be turned on or off instantly depending of the state of the individual [26]. In the cat anterogradely labeled fibers from the lumbosacral spinal cord form a dense terminal field particularly in the lateral PAG [24]. Furthermore, bladder and pelvic nerve stimulation evokes activation of the PAG [27]. The importance of the PAG in the cat is exemplified by the observation that electrical stimulation of the lateral PAG results in the cat in micturition which includes an initial relaxation of the external urethral sphincter (EUS) followed by a bladder contraction [28, 29]. Furthermore, the lateral and, to a lesser extent, the dorsal PAG projects specifically to the PMC [28]. It has been proposed that the basic micturition reflex contains an ascending pathway from the lumbosacral cord to the PAG and PMC and a descending pathway from the PMC to the sacral cord. Lesions between the PAG-PMC and the sacral spinal cord will result in a disruption of the normal micturition reflex and cause bladder-sphincter dyssynergia. Lesions of rostral from the mesencephalic PAG will result in the loss of control of the timing of micturition, but the micturition reflex remains intact. Although these circuits are based on animal models, a pivotal role for both the PAG and PMC has been confirmed in man using positron emission tomography and functional magnetic imaging with and without a full bladder [21, 22, 30–32].

5.2.4 Hypothalamus

Suprapontine and supramesencephalic afferents to the PAG and PMC are important to initiate or withhold micturition (pre-micturition phase) and could be targets for modulating bladder function. The most prominent afferents in the cat and rat are the lateral hypothalamus and medial preoptic area [33–35].

The lateral hypothalamus is involved in defensive responses. Modulation of the PAG and PMC by the hypothalamic afferents likely plays a role in urination as a component of the defense response [36, 37]. A second major afferent to the PAG and PMC arises from the medial preoptic area [33]. The hypothalamus was activated with dynamic PET imaging during micturition in humans [21, 22]. This area receives major projections from the dorsolateral prefrontal cortex and is thought to play a role in in the decision whether it is safe enough to start micturition via the PMC or unsafe and increase the contraction state of the urethral sphincter via the PCC [21].

5.2.5 The Role of Cortical Areas

The most common urinary symptoms in lesions of the cortical areas are urinary frequency and urgency urinary incontinence. Andrew and Nathan hypothesized on the basis of cerebral lesions in humans that disconnection of frontal or anterior cingulate gyrus from the hypothalamus results in involuntary start of micturition [38]. Indeed, the human prefrontal cortex and anterior cingulate gyrus are activated during micturition [21, 22, 32].

5.2.6 Cerebellum and Basal Ganglia

Several stimulation and lesioning studies in animals have shown that the cerebellum and basal ganglia have mainly an inhibitory action on the bladder during filling [2, 39, 40]. Cerebellar pathology in humans results in increased urinary frequency and urgency urine incontinence [41]. These overactive bladder symptoms are also found in Parkinson's disease [42]. Since there exist no direct projections from these areas to the PMC, the inhibitory influence is probably indirect via forebrain and midbrain structures.

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Overview of Neural Control of Bladder Storage and Voiding

6

Jalesh N. Panicker

6.1 Introduction

The lower urinary tract is distinct from other visceral organs due to its reliance on neural input from the central nervous system. A complex network distributed across the parasympathetic, sympathetic and somatic neural pathways, and controlled by different centres at the level of the brain stem acts as a switching circuit to maintain the functions of the lower urinary tract (LUT)-to coordiate low pressure filling and periodic voluntary emptying. This chapter provides an overview of this neural network.

6.2 The Peripheral Innervation Relevant to Lower Urinary Tract Control

The afferent and efferent signalling pathways responsible for control of the LUT is derived from the thoracolumbar sympathetic outflow, the sacral parasympathetic and sacral somatic nerves [1]. The sacral outflow in humans is considered to belong to the parasympathetic system, however this has recently been questioned in a study that evaluated phenotypic and ontogenetic features distinguishing pre- and post-ganglionic neurons of the cranial parasympathetic outflow from those of the thoracolumbar sympathetic outflow in mice which suggested that the sacral outflow is indistinguishable from the sympathetic thoracolumbar outflow [2]. The pre-ganglionic parasympathetic nerves are derived from the intermediolateral column of the sacral cord, predominantly S2,3,4 segments. Short post-ganglionic fibres destined for the bladder arise from the ganglia in the pelvic plexus and innervate the detrusor. These postganglionic parasympathetic nerves release acetylcholine (ACh) in the detrusor at the neuromuscular junction, which acts on muscarinic receptors, principally M3, and M2, resulting in detrusor contraction and bladder emptying [3, 4]. Excitatory neurotransmission also occurs through a non-cholinergic system, whereby ATP, acting as a transmitter substance, acts on P2X receptors [4]. The parasympathetically mediated inhibitory signalling to the urethral smooth muscle is via nitric oxide (NO) release which causes relaxation [4].

The sympathetic and somatic innervation, on the other hand, promote urine storage, by relaxing the detrusor and providing an excitatory input to contract the urethral smooth (sympathetic) and striated (somatic) muscle. The pre-ganglionic sympathetic outflow originates from the intermediolateral column of the thoracolumbar cord, predominantly T11-L2. The hypogastric nerve, a postganglionic sympathetic nerve, activates inhibitory β-adrenergic receptors in the detrusor, with the release of noradrenaline, resulting in relaxation of the detrusor [4]. The sympathetic receptors in the bladder neck and smooth muscle of the urethra are excitatory α-adrenergic. Somatic outflow is derived from a cigar-shaped hybrid nucleus in the anterior horn of the sacral cord, predominantly S1,2,3 segments, known as the Onuf's nucleus. Axons constitute the pudendal nerve and innervate pelvic floor muscles and the external (striated) urethral sphincter [4].

The afferent signals from the bladder travel through the parasympathetic pelvic nerves and hypogastric nerves [1]. These fibres convey sensations of the degree of bladder fullness. Afferent signals from the bladder neck and urethra are conveyed to the spinal cord through the pudendal and hypogastric nerves. There are two nerve fibre types—Aδ (thinly myelinated) and C (unmyelinated) fibres. The cell bodies of these nerves are present at the level of S2-4 and T11-L2, in the dorsal root ganglia (DRG). Here these nerves synapse with interneurons which either transmit messages to spinal neurons, that connect with higher brain centres, or with neurons involved in polysynaptic spinal reflexes at the level of the lower spinal cord [4]. The Aδ fibres are of functional significance in health and are sensitive to mechanical stimuli such as distension and stretch. C-fibres comprise upto

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_6

two-thirds of bladder afferent nerves, and tend to be dispersed more widely—in the detrusor, suburothelium and adjacent to urothelial cells. Also termed 'silent' or 'dormant' fibres, they are insensitive to physiological filling, but respond to noxious stimuli, provide nociception and are sensitive to changes in temperature and pH. It is these nerves that are thought to be important in the pathogenesis of urgency and OAB following neurological injury [5].

Functional imaging studies, that are covered elsewhere, have identified several neuronal populations in the brain that are thought to be important in the control of micturition. These areas include the pontine micturition centre (Barrington's nucleus, PMC), located in the dorsal tegmentum of the pons, and the periaqueductal grey (PAG) of the midbrain, serotonergic nerves in the medullary raphe nuclei, the noradrenergic nerves of the locus coeruleus and the A5 cell group in the brain stem. These higher centres are connected through interneurons to the lumbosacral cord [4]. Neurons in the PMC receive input from the hypothalamus and PAG, and axons descend through the spinal cord to the parasympathetic nucleus in the sacral cord.

6.3 Neural Control of Storage

The bladder functions as a reservoir in health, storing urine for 99% of the time, maintaining continence [4]. This is achieved through the co-ordinated inhibition of parasympathetic activity thereby relaxing the detrusor, and tonic contraction of the urethral smooth and striated sphincters [6]. Sympathetic mediated activation of beta-3 adrenoceptors play an important role during storage [7]. Urinary storage is achieved by activity from different centres in the brainstem, namely the PMC and the PAG. The control of micturition is under voluntary control, which is learned and develops with maturation of the central nervous system and the emergence of different cortical and subcortical regions that influence activity of the PAG and PMC. In health, when the bladder reaches 200–400 mL volume, the sensation of filling and urge to void is relayed to the brain via the spinal cord. During storage, a low level of activity through sacral afferent fibers stimulates reflex stimulation of the sympathetic and somatic efferent fibres innervating the smooth and striated elements of the bladder outlet, respectively, thereby maintaining continence [1]. This afferent activity is thought to form the basis for the pro-continence guarding reflex [8]. The parasympathetic activity remains quiescent during this period, allowing relaxation of the detrusor smooth muscle. During filling, a population of PMC neurons are turned 'off', however there is a level cut-off level of distension at which the afferent activity from tension receptors can switch 'on' these cells, initiating a spinobulbospinal voiding reflex.

To ensure that bladder emptying occurs only at the appropriate times, cortical centres such as the prefrontal cortex, suppress excitatory signals to the PMC, and delay voiding until a more socially appropriate time [4]. The insula appears active in imaging studies of urine storage, and plays an important role in the conscious perception of bladder fullness [9].

6.4 Neural Control of Voiding

When it is deemed appropriate to void, the PMC is released from the tonic inhibition of the cortical and sub-cortical regions, and the PAG plays a critical role in the release of this inhibition [1]. Recordings from cats have shown several neuronal populations within the PMC to exhibit firing at different times during the micturition cycle. Some of these are termed direct neurons, which fire prior to, and during reflex bladder contraction. Another group are termed inverse neurons which are active during the periods between bladder contractions, and yet a third group are termed on-off neurons which fire at the beginning and end of the bladder contractions [10]. Only a few of the inverse neurons project to the lumbosacral cord, and so it is thought that they may have a local inhibitory function in the PMC.

The frequency of micturition in an individual with a bladder capacity of 400–600 mL is once every 3–4 h and voiding lasts only 2–3 min per 24 h. When the bladder is full, activation of a bladder-to-urethra inhibitory reflex interrupts urethral activity, and this is followed by a bladder-to-bladder excitatory reflex which promotes detrusor contractions [11]. Descending efferent activity from the PMC results in parasympathetic-mediated contraction of the detrusor. Simultaneously, release of sympathetic and somatic activity results in relaxation of the pelvic floor muscles and sphincters. In addition to the release of adrenergic and cholinergic excitatory inputs, urethral smooth muscle relaxation is facilitated by the release of nitric oxide, as well as parasympathetic mediated activity.

6.5 Neurotransmitter Systems

Numerous neurotransmitter systems are thought to be involved in the control of micturition. These include excitatory substances such as including glutamic acid, tachykinins, nitrous oxide, and ATP. Glutamic acid acts on *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors, and appears to be an essential transmitter in spinal and supraspinal reflex pathways [12]. Inhibitory amino acids glycine and γ-aminobutyric acid (GABA), and opioid peptides (enkephalins), exhibit an inhibitory control in the PMC. Other

receptors can behave in an excitatory or inhibitory manner, depending on the type and location of the receptor in the CNS. These include dopamine, serotonin, 5-hydroxytryptamine (5-HT), noradrenaline, ACh, and non-opioid peptides.

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Part III

Physiology and Pharmacology

The Integrated Physiology of the Lower Urinary Tract

7

Chris Fry and Rita Jabr

7.1 Functions of the Lower Urinary Tract (LUT)

The lower urinary tract consists of the bladder and outflow tract. For most of the time the LUT serves a storage function, whereby the bladder fills with urine from the ureters whilst maintaining a low intraluminal pressure and the outflow tract offers a high fluid resistance to maintain continence (Fig. 7.1). At regular intervals voiding occurs when the bladder wall contracts, to raise intraluminal pressure, and the outflow tract relaxes. Furthermore, the LUT is supported by a pelvic floor musculature. It does not have an active role in storage and voiding but when it is dysfunctional can contribute to LUT disorders. This relatively simple micturition cycle however demands a number of conditions:

- Reflux of urine into the upper tract (ureter and renal pelvis) must be prevented otherwise raised upper tract pressures could cause ureteric dilatation (hydronephrosis) and renal damage. This is achieved by: ensuring the bladder has a high filling compliance, i.e., the bladder can accommodate large volumes of urine (up to 500 mL) with small changes of intraluminal pressure (<10 cm H_2O); maintaining an anatomical ureteric-vesical junction that acts as a unidirectonal valve.
- The inverse relationship between intraluminal bladder pressure and outflow tract resistance during filling and voiding must be carefully synchronised otherwise continence will not be maintained in filling, or the bladder will contract against a high outflow resistance and risk incomplete voiding. This is achieved by neural synchronisation of muscular elements in the outflow tract—particularly skeletal muscle in the rhabdosphincter—and in the bladder wall—detrusor smooth muscle (see Sects. 1.3 and 2.2).

The integrated nervous control of the lower urinary tract is considered in Sect. 1.2. The purpose of this chapter is to give the reader an introduction to the important components of the LUT, and associated structures such as the pelvic floor musculature. The aim is to consider how the component parts, and their cellular and extracellular elements, work individually or together to determine the normal and abnormal functions of the LUT. Cellular and intracellular pathways will not generally be described in detail and the reader will be referred to other sources as necessary, except where such information is sparse.

7.2 Detrusor Pressure, Bladder Wall Tension and Detrusor Contractility

Figure 7.1 shows a urodynamic trace of subtracted detrusor pressure, P_{det} ($P_{ves} - P_{abd}$: P_{ves} = intraluminal pressure, P_{abd} = abdominal or rectal pressure, cmH_2O) during filling and voiding. During bladder filling, of volume V (mL), bladder compliance, C, can be estimated from the change of P_{det},

$$C = \Delta V / \Delta P_{det}, \text{ with units of } mL / cmH_2O. \qquad (7.1)$$

Voiding is initiated by a rapid rise of P_{det}—the inset shows that initially the bladder contracts isovolumically before outlet resistance is overcome to initiate flow.

Urodynamic traces, as shown in Fig. 7.2a with examples of overactive contractions and an evoked response, are not straightforward to interpret in terms of muscle mechanics for two reasons:

- P_{det}, is dependent not only on bladder wall tension, T, generated by passive stretching or active muscular contraction, but also on the dimensions of the bladder itself. If it assumed that the bladder is spherical then wall tension

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_7

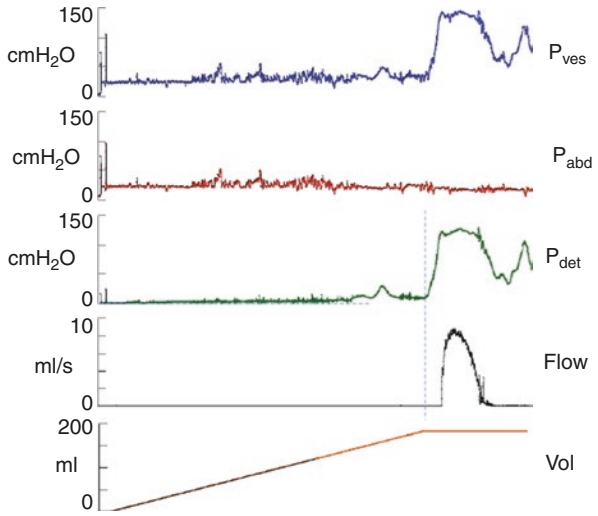

Fig. 7.1 Urodynamic traces. Example of a man with evidence of outflow tract obstruction. Traces from the top are: intravesical pressure (P_{ves}); rectal (abdominal) pressure (P_{abd}); subtracted detrusor pressure ($P_{det} = P_{ves} - P_{abd}$); urine flow; filling volume. The horizontal dotted line on the P_{det} trace is baseline pressure before filling and the slope of the trace can be used to measure filling compliance (see text). The vertical dotted line shows the delay between the rise of P_{det} and the initiation of voiding. With thanks to Mr. Andrew Gammie, Bristol Urological Institute, North Bristol NHS Trust for access to urodynamics traces

and intraluminal pressure are related by Laplace's Law, where r is bladder radius and d the thickness of the bladder wall. Figure 7.2b shows measured values of P_{det} during a voiding contraction and estimated values of contractile function (wall tension). Values of these two variables are normalised to their maximum values, which are achieved in the isovolumic phase just prior to voiding. Thereafter, as voiding occurs the contraction (wall tension) declines but P_{det} is maintained due to the reduction of bladder volume and hence the value of r. In this calculation bladder wall thickness was assumed to increase from 3 to 5 mm. Thus the maintenance of P_{det} is due to the extent of emptying.

$$P = 2Td / r \qquad (7.2)$$

- The magnitude of a change of P_{det} is dependent not only on the contractile state of the muscle, but whether voiding is occurring or not. An often-misused term in urology is the word 'contractility' and can be used to indicate changes to P_{det}. However, as indicated above P_{det} can differ according to bladder volume and be unrelated to changes in muscle performance. In addition, as seen from Fig. 7.2a, a voiding and an overactive contraction from the same bladder can generate different peak P_{det}—the overactive contraction in this instance is greater. One difference in the two states is that the overactive contraction is against a closed sphincter, whereas with the voiding equivalent, the energy of contraction is partly used to generate flow so that less is consumed in merely generating a rise of P_{det}.

The contractility of smooth (or cardiac) muscle has a specific meaning, namely an alteration of the contractile (or inotropic) state of the muscle independent of resting length, as resting length itself alters the strength of contraction as demanded by the sliding-filament hypothesis. The concept was first introduced with respect to cardiac function, as the strength of the heart beat can be dependent on diastolic filling (and hence the myocyte resting length) or its inotropic state. It is important to distinguish between the two as reduced ventricular stroke work may be due to reduced diastolic filling (e.g., with hypovolaemia) or a reduction of myocyte contractility (e.g., with myocardial ischaemia). Distinguishing between the two is essential as it determines the therapeutic management of the patient. Thus, in the bladder a symptomatic concept of underactive bladder has recently been proposed [2], but its clinical definition provides little help as to its pathogenesis. Fortunately, lessons learnt from cardiology can be used to decide whether a smaller change of P_{det} is likely to arise from a true change of contractility, or from some other cause such as a change to outflow resistance, loss of muscle mass or different filling volume [3]. The procedure involves transforming the isometric (or isovolumic for pressure) rising phase of a contraction (except for the initial 10% of the trace) as shown in Fig. 7.2c where each value of P is plotted against the instantaneous value of $(dP/dt)/P$. The resulting plot is similar to a Hill force-velocity relationship with the intercept on the y-axis, v_{max}, a measure of true contractility (maximum shortening velocity of muscle fibres, the curve-fit is of an hyperbola). The plot is sensitive to the addition of inotropic agents such as carbachol [4]. Shown also are v_{max} values from the overactive and voiding contractions shown above, where the contractility of the bladder is actually less than during the voiding contraction, the greater peak value of P_{det} with the overactive contraction is due to the fact that energy was not being dissipated in ejecting fluid. Although, the transformation looks complex to analyse the values of v_{max} are empirically associated with some urodynamic variables and hence measurement of true detrusor contractility is practical [4].

7.3 Extracellular Matrix and Biomechanics of the Bladder Wall

The compliance of the bladder wall can alter under many LUT pathologies. A decreased compliance will result in a more rapid rise of P_{det} during filling that can manifest as any combination of more frequent voiding; increased urgency; overflow incontinence and raised upper tract pressures. Alternatively, an

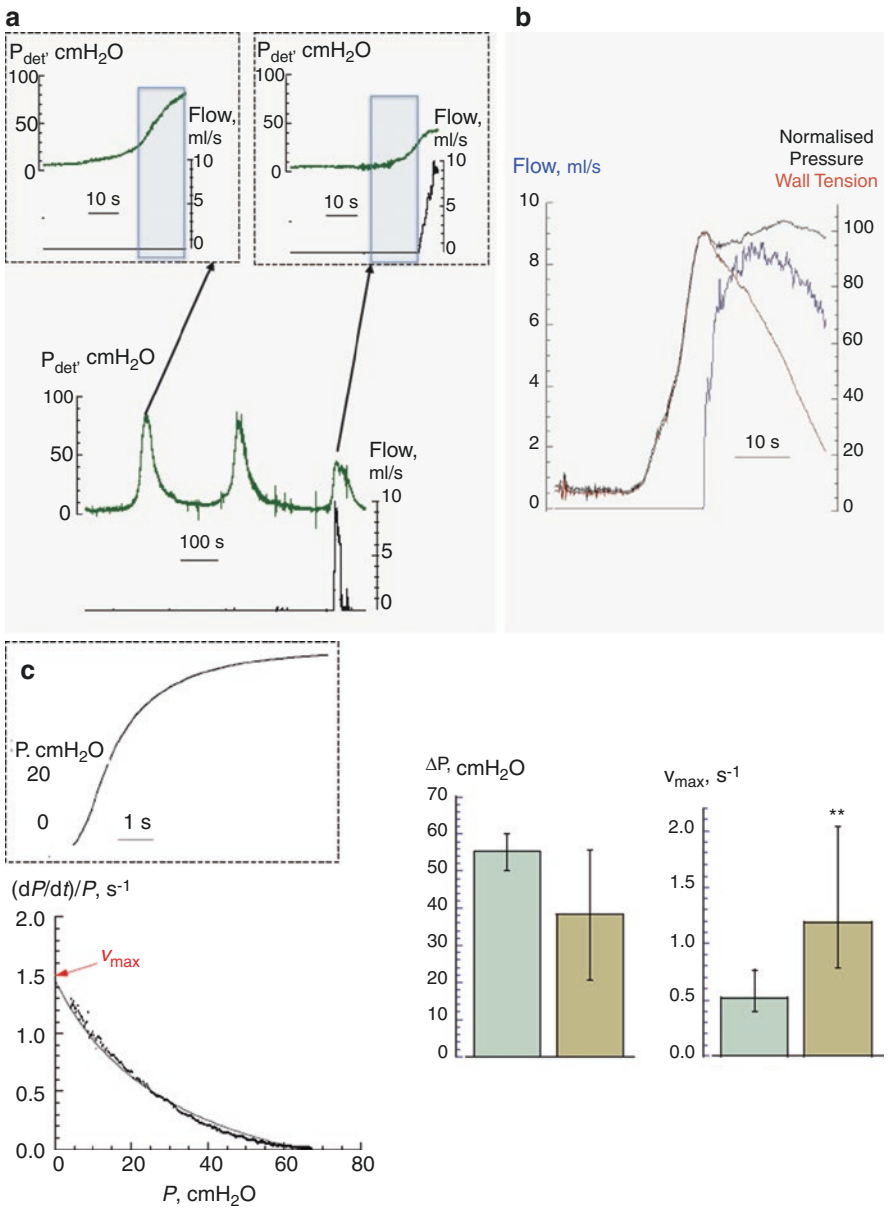

Fig. 7.2 Urodynamic traces used to estimate bladder contractility. (**a**) Example of a urodynamic trace of P_{det} and urine flow from a patient showing two overactive contractions before a voiding (evoked) contraction. The two insets show the isovolumic rising phases of P_{det} of the overactive and voiding contractions (boxed areas). With the voiding contraction this phase is between the onset of the rise of P_{det} and the initiation of voiding itself. (**b**) Values of P_{det} (pressure) and estimated wall tension using Laplace's Law during an evoked contraction. Pressure and Wall Tension have been normalised to the maximum value of the respective variables which was achieved just prior to the initiation of voiding. P_{det} was maintained after voiding despite the fall of estimated wall tension due to the reduction of bladder volume. Bladder wall thickness assumed to change from 3 to 5 mm during the period of bladder emptying. (**c**) Left; estimation of bladder contractility, v_{max}, from the isovolumic region of the rise of pressure P. The pressure curve is transformed so that values of (dP/dt)/P are plotted against P itself throughout this period and the value of v_{max} estimated from a fit of the data to a hyperbola [1]. Right: Values of the maximum increase of P_{det} (ΔP) during the respective contractions, and the corresponding v_{max} values. $^{**}p < 0.01$ overactive vs. evoked contractions. With thanks to Mr. Andrew Gammie, Bristol Urological Institute, North Bristol NHS Trust for access to urodynamics traces

even greater compliance will result in greater filling volumes and potentially weaker bladder contractions. Whatever the shift, a change from normal compliance can have potentially pathological effects on bladder function. Generally, altered compliance results from changes to the amount and composition of extracellular matrix (ECM), a complex of collagen and elastin fibres within a ground substance. Changes to collagen content has received the most attention as it is the most abundant extracellular protein with two subtypes, collagen-I and -III, importantly contributing to the biomechanical properties

of tissue. In the normal bladder wall most extracellular matrix is confined to the suburothelial layer—between the urothelium itself and the detrusor layer—but with increased deposition of ECM this spreads also to the detrusor layer between muscle bundles. In the normal bladder the collagen-I to -III ratio is greater than unity, but with pathologies leading to greater ECM deposition (e.g., outflow obstruction, neurogenic lesions, radiation damage) the relative amount of collagen-III increases [5]. Generally collagen-I fibrils are stiffer than collagen-III [6] and so some of the variations in bladder wall compliance observed in different animal models and human conditions may reflect the opposing effect of a greater collagen deposition *per se* and a shift in the collagen subtype. A large increase of compliance seen in several late-stage animal models may reflect also an excessive deposition of ground substance.

The archetypal collagen-producing cell is the myofibroblast, which can be transformed from a number of other cells in the bladder wall, including fibroblasts, epithelial cells and even smooth muscle cells [7]. Of particular importance in this transformation is local production of TGF-β under physical and chemical stresses [8], augmented by input from the *wnt*-signalling pathway [9]—Fig. 7.3a. TGF-β levels are augmented in many conditions associated with excessive ECM deposition, such as bladder outflow obstruction; ischaemia; and neurological lesions. Not only is myofibroblast differentiation increased under these conditions, but expression of matrix metalloproteinases (MMP) is decreased and that of a tissue inhibitor of MMP increased [10]. A considerable research effort is currently underway to understand the pathways that control ECM deposition and possibly its reversal and while there have been successes in pathologies such as pulmonary fibrosis and portal hypertension [11, 12], the situation with modulating bladder wall fibrosis is currently less advanced.

Whilst there is good histological and molecular evidence of ECM deposition and altered bladder wall compliance there is less work on the relation of bladder compliance to biomechanical stiffness measurements. In vitro bladder wall stiffness is parameterised by measuring the change of internal tension (stress, σ, usually normalised to cross-section area) when the tissue is stretched (strain, ε, usually expressed as a proportion of the resting strain). Tissue stress increases with increased strain and after a period of partial, viscoelastic relaxation a greater steady-state stress is achieved. The ratio of steady-state stress to strain is a measure of tissue stiffness—the elastic or Young's modulus—Fig. 7.3b. Experiments have concluded that bladder wall tissues with a greater ECM proportion are stiffer (less distensible or compliant) than normal tissue. It may be concluded that low compliance bladders are associated with greater ECM deposition [29]. Thus, the above search for antifibrosis therapies should be successful in

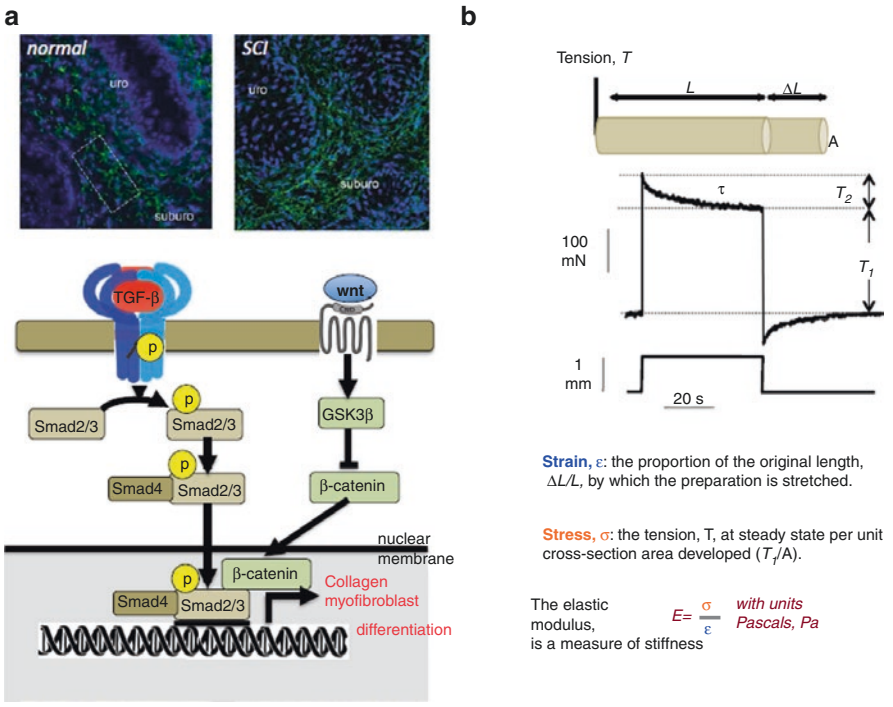

Fig. 7.3 Interstitial cells (myofibroblasts) and muscle mechanics. (**a**) Top; confocal images of rat bladder urothelium (uro) and suburothelium (suburo)—interstitial cells in normal and spinal cord injury (SCI). Cx43 labelling (green) is used as a marker for interstitial cells. Magnification ×400; modified from Ikeda et al., 2007. Bottom: intracellular pathways for TGFβ and *wnt*-proteins to augment myofibroblast differentiation and then collagen production. (**b**) Procedure to estimate tissue stiffness of isolated preparations. Passive stretch (strain) of a preparation generates an increase of tension (stress) that exhibits some visco-elastic relaxation with magnitude T2 and time constant τ. The steady-state tension, T_1, normalised to the cross-section area, A, of the preparation is used to estimate the elastic modulus (stiffness), E

restoring the poorly compliant bladder towards the normal state. The situation with very compliant (underactive) bladders is poorly understood at present.

7.4 The Initiation of Detrusor Contraction

Voiding contractions are initiated by activation of postganglionic parasympathetic nerves with terminals that are evenly distributed throughout the detrusor layer. These efferent nerves release both acetylcholine (ACh) and ATP, possibly from different vesicles in the nerve terminal as the characteristics of their release differ in important aspects: ATP is preferentially released at low stimulation frequencies and the release of ATP and ACh can be separately regulated, i.e., ATP release can be selectively reduced by adenosine (A1) receptor agonists [13]. Detrusor contractions of tissue from normal human bladders (and old-world monkeys) differ from those of other species in being completely dependent on nerve-released ACh (there is no atropine resistance—Fig. 7.4a). In other species there is an atropine-resistant component to the contraction, itself abolished after administration of agents such as ABMA (α,β methylene-ATP) that desensitise purinergic (P2X) receptors. Of interest is that an atropine-resistant component of human detrusor contraction is also present in tissue from children's bladders and from adults with overactive or obstructive bladder symptoms [14, 15]. Atropine resistance may be explained by differences in the rate of ATP hydrolysis in the nerve-muscle junction by ecto-ATPases, with breakdown greater in normal human detrusor, so that none is available to activate the detrusor muscle membrane [16]. The ability to reduce selectively ATP rather than ACh release from motor nerve terminals offers a potential therapeutic route to reduce selectively the component of contraction associated with overactive and obstructed bladder pathologies.

ATP and ACh mediate different intracellular pathways to generate contraction. ATP binds to an ionotropic $P2X_1$ receptor, a non-specific cation channel, to initiate cation influx and membrane depolarisation. The subsequent activation of L-type Ca^{2+} channels increases intracellular Ca^{2+}, augmented by Ca^{2+}-induced Ca^{2+} release form intracellular stores, to initiate contraction [17]. ACh binds to muscarinic receptors, the major functional subtype being M3 in detrusor [18]. However, M2 receptors are more abundant and suggests that M3 receptors may be preferentially clustered around the nerve-muscle junction. The intracellular pathways activated by the Gq protein-coupled M3 receptor have some complexity and may differ between species [4, 19]. In human tissue the generation of the second messenger IP_3 (inositol trisphosphate) that subsequently releases Ca^{2+} from intracellular stores has been identified. But it is argued that the concentrations of M3 receptor agonists required for such a pathway is high and may be important for a population of M3 receptors

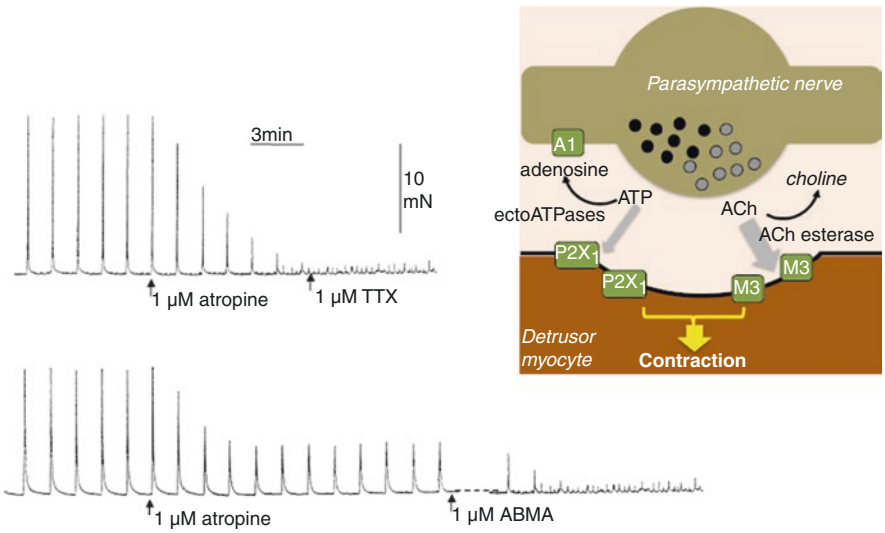

Fig. 7.4 Neuromuscular transmission at the nerve-detrusor muscle junction. *In vitro* contractions of human detrusor strips from patients with: a functionally normal bladder (upper tracing) and idiopathic detrusor overactivity (IDO, lower trace). Each upward deflection is a contraction evoked by electrical field stimulation (EFS) every 90 s, except the small irregular spontaneous contractions at the end of each trace. With the normal bladder trace addition of atropine abolished completely the EFS contraction. The neurotoxin TTX (tetrodotoxin) has no further effect on the spontaneous contractions. With the IDO bladder trace atropine only partially reduced the contraction, the remainder was abolished by treatment with ABMA (α,β methylene-ATP) to desensitise purinergic receptors (the break in the trace omits the brief contraction elicited by ABMA before desensitisation. The inset shows a model for transmission at the nerve-detrusor junction. Acetylcholine (ACh) and ATP are released from nerves and can bind to respective M3 or $P2X_1$ receptors on the muscle membrane. Receptor activation is offset by partial or complete breakdown by enzymes facing the junctional space (acetylcholine esterase or ectoATPases respectively). The breakdown product of ATP—adenosine—exerts a negative feedback control of further ATP release *via* an A1 receptor

distant from the nerve-muscle junction. A set of junctional M3 receptors also activates L-type Ca^{2+} channels to initiate Ca^{2+} influx and augment further intracellular store release of Ca^{2+} *via* Ca^{2+}-induced Ca^{2+} release. At the same time Ca^{2+}-sensitisation of the contractile proteins occurs *via* activation of protein kinaseC and Rho-kinase pathways. In this context, the ability of β3 adrenoceptor agonists to relax detrusor muscle is important as this has permitted introduction of β3 agonists, such as mirabegron, as a new class of agents to reduce overactive bladder symptoms [20].

7.5 Electrophysiology of Detrusor Smooth Muscle

Detrusor smooth muscle is an excitable tissue and can generate regenerative action potentials that initiate from a resting potential around −50 to −60 mV. The resting potential is positive with respect to activation for Na^+ channels but negative for L-type and even T-type Ca^{2+} channels. Thus, the depolarising phase of the action potential is carried by Ca^{2+} channels predominantly through L-type channels. The current density of L-type Ca^{2+} current is high and this coupled to the relatively large surface-to-volume ratio of detrusor smooth muscle cells compared to say cardiac myocytes means that Ca^{2+} influx through Ca^{2+} channels can raise substantially the intracellular Ca^{2+} concentration, $[Ca^{2+}]$, to support a contraction. T-type Ca^{2+} channels are activated at more negative membrane potentials than L-type channels, near to the resting potential, which suggests that they could have a pacemaking role and hence produce spontaneous activity. Indeed T-type channel activity is greater in human detrusor from overactive bladders and may indeed contribute to greater myogenic activity [21, 22]—Fig. 7.5a. Repolarisation is mediated via K^+ channels and several types have been recorded including large and small conductance Ca^{2+} activated K^+ channels (BK and SK channels), ATP-sensitive K^+ (K_{ATP}) channels and several voltage-activated K^+ channels [23]. Overall the large current density of K^+ channels, and the importance of Ca^{2+} activated channels, explains the ability of detrusor to sustain a relatively high frequency of action potential generation that may sustain localised spontaneous activity.

Detrusor smooth muscle also expresses gap junction proteins, connexins (Cx), which indicate electrical coupling between individual myocytes is possible. Several Cx subtypes exist and that in detrusor is mainly Cx45. Another subtype Cx43 is also found in the detrusor layer and is a feature of interstitial cells between muscle bundles, but there are reports it is also found in detrusor muscle itself [21, 22]. Connexin proteins are components of gap junctions between contiguous cells and their presence suggests that electrical

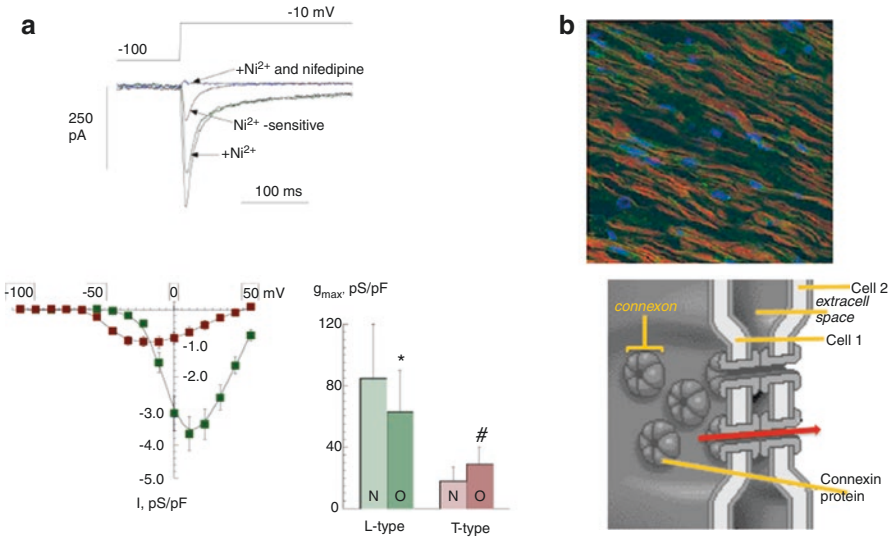

Fig. 7.5 Electrophysiological mechanisms in detrusor smooth muscle. (**a**) Inward Ca^{2+} currents recorded from human detrusor smooth muscle (Cs-filled electrodes to suppress K^+ currents). Upper traces: part of the current is suppressed by 100 μM $NiCl_2$ (brown trace) to leave a Ni^{2+} resistant component (green trace) that itself is abolished by 5 μM nifedipine (blue trace). The Ni^{2+} sensitive component is shown to be a T-type Ca^{2+} current and the Ni^{2+} resistant component an L-type Ca^{2+} current. Lower plots: (left) current-voltage-relationships of the T-type (brown) and L-type (green) Ca^{2+} currents; (right) the maximum conductance of the L-type and T-type currents in cells from normal (N) and overactive (O) bladders. T-type current, which has a more negative activation range, is increased in overactive bladder myocytes. *$p < 0.05$ vs. normal for L-type; #$p < 0.05$ vs. normal for T-type currents. Modified from Sui et al., BJUInt 2006;99:46–41. (**b**) (Upper) confocal images (magnification ×400) of rat detrusor muscle confocal image: Cx45 labelling (green) is associated with detrusor myocytes (red). Nuclei labelled with DAPI (blue). (lower) Model of a gap junction between two adjacent cells. Six connexin proteins comprise a connexon. Two connexons from adjacent cells form a gap junction that allow transfer of electrical signals and small molecules between the intracellular compartment of the two cells

signals can propagate between cells generating a functional syncytium, Fig. 7.5b. The different Cx isoforms form gap junctions of different electrical properties, with Cx45 have a lower electrical conductance compared to those formed of Cx43 for example. The consequence is that propagation of electrical signals will be slower *via* gap junctions of lower electrical conductance. In the heart an abundance of Cx43 gap junctions (and of even larger conductance Cx40 gap junctions in atria) at the intercalated disk ensures that large volumes of myocardium can act as a functional syncytium. Detrusor smooth muscle is composed of muscle bundles separated by extracellular matrix so that extensive electrical activity will be of less importance. It is likely that detrusor gap junction will ensure that individual cells in a muscle bundle can be synchronised, whilst coordination of activity in the detrusor mass relies on the extensive distribution of parasympathetic nerve fibres. The role of interstitial cells that lie between detrusor muscle bundles is contentious; electrical and intracellular Ca^{2+} transients are not synchronised with similar events in detrusor cells, but they may provide a link between activity in adjacent muscle bundles [24].

7.6 Interstitial Cells in the Bladder Wall

These cells are found throughout the detrusor layer and especially the suburothelium, Fig. 7.6. A potential role in the detrusor layer has been discussed, but there has been a focus if interest of their role in the suburothelium [25]. It is noteworthy that the density of suburothelial interstitial cells increases in pathologies associated with detrusor overactivity and so a causal link has been suggested if not decisively shown [26–28]. Several sub-populations exist that may vary according to normal or pathological conditions and have different signalling pathways, for example in the suburothelium, in intradetrusor spaces and surrounding blood vessels. Moreover, it is suggested that those with a myofibroblast phenotype are more abundant in the suburothelium adjacent to the urothelium itself [29], and that their number is raised in conditions that have increased collagen deposition. A problem with identifying different subpopulations is that characteristic markers are not universally agreed and range from more generalised mesenchymal labels such as vimentin, to α-smooth muscle actin through to more specific labels such as c-kit and PDGF-α. Some of the literature add "…of Cajal" to 'interstitial cell'. It is the authors' opinion that this should be avoided as it implies that interstitial cells in the bladder wall have a pacemaking function, as in the G-I tract, and there is no evidence for an equivalent function in the bladder.

However, there are some features of bladder interstitial cells that may point to some specific functions. For example: (a) they are electrically excitable with depolarisation mediated by Ca^{2+}-activated Cl^- channels or Ca^{2+} channels and generate associated intracellular Ca^{2+} transients in response to a wide range of activators such as ATP and its metabolites as well as low pH [30]. This coupled to extensive Cx43 gap junctions between cells suggests that those in the suburothelium may form a functional syncytium (see below under *Spontaneous Contractions*); (b) in the suburothelium they make intimate contact, although with no gap junctions, with afferent nerves [31]. It is possible that these cells transduce

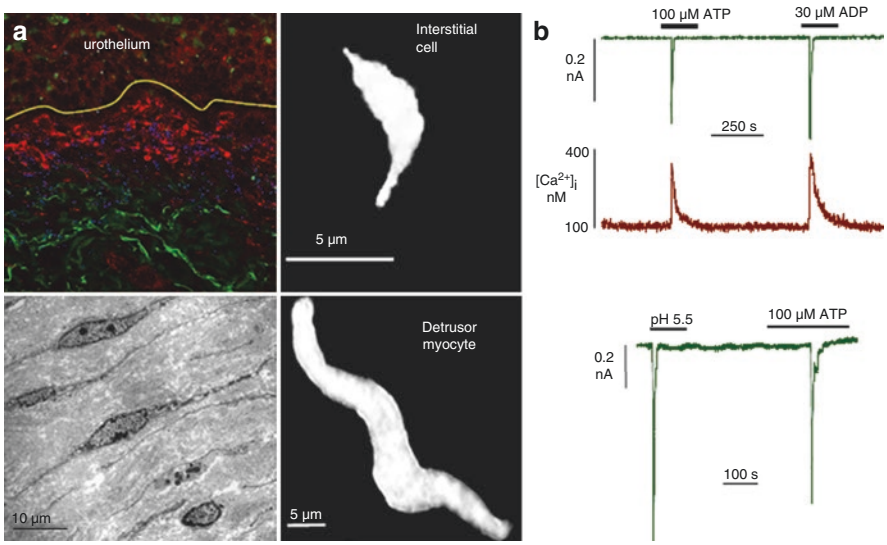

Fig. 7.6 Interstitial cells from the suburothelium. (**a**) Top left: urothelium and suburothelium labelled for vimentin (red) and Cx43 (blue). Collagen autofluorescence (green). The yellow line demarcates urothelium from suburothelium. Bottom left: electron micrograph of the suburothelium showing interstitial cells. Right: isolated interstitial cell and detrusor mycocyte to demonstrate size difference. (**b**) Total ionic current (green) and intracellular Ca^{2+} (brown) from isolated interstitial cells. Shown are responses to purines and low pH

or amplify the action of neuromodulators released from the urothelium that ultimately activate afferent nerves. More extensive descriptions of the cellular properties of interstitial cells are found in [4, 32].

7.7 Spontaneous Contractions and the Relation to Detrusor Overactivity

The bladder is able to generate spontaneous contractile activity at every organisational level from the bladder within the body [33] through to isolated organs [34]—Fig. 7.7a; sheets of tissue; small isolated tissue bundles [35]—Fig. 7.7b and even isolated detrusor cells—Fig. 7.7c.

In the normal bladder it has been proposed that such activity during filling sets a background level of tonus to the bladder that is not too great to compromise a high bladder compliance but sufficient to allow the bladder to rapidly increase wall tension when necessary. It has also been tempting to speculate that such spontaneous activity, if increased and synchronised across the bladder, may provide a basis for detrusor overactivity, although this is more difficult to demonstrate. Isolated tissue experiments also show that spontaneous contractile activity is not confined to detrusor muscle, but is also found in preparations of mucosa (urothelium and suburothelium). Another consistent observation is that isolated detrusor preparations show little spontaneous activity, but that the presence of the mucosa greatly enhances this activity.

Several not-mutually exclusive, hypotheses have been proposed for spontaneous activity:

- ***A myogenic theory*** that proposes detrusor muscle itself generates spontaneous electrical and intracellular Ca^{2+} transients and hence contractions. Such phenomena have been recorded in isolated myocytes, more when they come from overactive bladders.
- ***A neurogenic theory*** that proposes increased peripheral nervous activity under conditions such as central nervous system damage and possibly due to loss of central inhibitory control. However, it has to explained why spontaneous activity, at least *in vitro*, is largely resistant to nerve blockers such as tetrodotoxin or antimuscarinics such as atropine. For a neurogenic hypothesis to be contributory, overactive bladder contractions would not be related to *in vitro* spontaneous activity and this disconnect has not been resolved.
- ***A mucosa theory*** that contractile elements here contribute to bladder wall spontaneous activity. This cannot be the whole story as the magnitude of such activity is less than when an intact mucosa is connected to detrusor. However, it may be a contributor and contractile elements can exist in the *muscularis mucosa*, the copious microvasculature and interstitial cells. Mucosa spontaneous activity may be driven in part by ATP release, possibly from the urothelium.

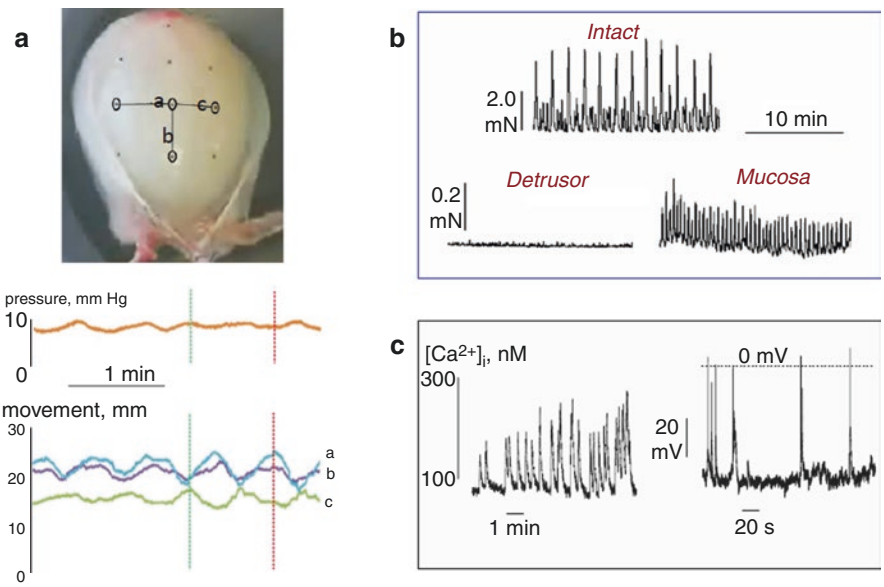

Fig. 7.7 Spontaneous activity. (**a**) Micromotions of the isolated rat bladder. The movements along the vectors, *a*, *b*, *c* are shown below, as well as variations of intravesical pressure. (**b**) Spontaneous contractions measured in isolated strips of bladder wall (intact); detrusor with the mucosa removed; mucosa alone—note the different vertical calibration bars for 'intact' versus 'detrusor' and 'mucosa'. (**c**) Spontaneous intracellular Ca^{2+} transients (left) and action potentials (right) in isolated human detrusor myocytes. Data courtesy of: part A, B Vahabi & M Drake; part B, N Kushida; part C, GP Sui

- ***A mucosa-detrusor theory*** that communication between the mucosa and detrusor layers enhances detrusor activity. Some have called this a urotheliogenic hypothesis but the name is not widely used, largely because it is difficult to pronounce!

The mucosa-detrusor hypothesis is gaining increasing traction and a key question is if interaction between the two layers is cellular or *via* diffusible agents. There is evidence for a cellular interaction from optical imaging experiments [36]. These show that spontaneous electrical and intracellular Ca^{2+} transients: (a) originate in the suburothelium and conduct rapidly in this layer and more slowly to the detrusor; (b) in overactive compared to normal bladders originate from fewer but more intense sources and correlate with less frequent but larger pressure transients; (c) dramatically decrease when the mucosa is removed; (d) are enhanced by P2Y agonists that have little effect on the detrusor but excite interstitial cells; (e) are enhanced by very low (50 nM) carbachol concentrations that have no direct effect on the detrusor but enhance urothelial ATP release; (f) are susceptible to attenuation by gap junction blockers. Another mode for the mucosa-detrusor theory is an excessive release of urothelial neuromodulators such as ACh or ATP. Urothelial release of ATP is augmented in pathological bladder conditions [37] and this could augment purely spinal or spino-bulbo-spinal reflexes. Moreover, urothelial release of ATP is likely to be controlled by prior stress- activated ACh release and so variations in its release pathway through the CFTR pathway will ultimately affect the sensory process [38, 39]. Control of urothelial ACh and ATP release as a modulator of abnormal lower urinary tract function via a mucosa-detrusor control pathway could also be an important mode of action for antimuscarinic agents and botulinum toxin. Both agents will impact on urothelial ATP release: antimuscarinic agents through a muscarinic control of ATP release through M2 receptors [39]; botulinum toxin through reduction of vesicular ATP release [40].

7.8 The Outflow Tract

7.8.1 Trigone

The trigone, the smooth muscle and supporting tissues of the urethra, as well as the skeletal muscle of the external urethral sphincter (the rhabdosphincter) comprise a co-ordinated outflow tract that maintains continence during filling and facilitates voiding when necessary.

The trigone is a triangular region of the bladder between the ureteric orifices and he bladder neck. It exhibits vigorous spontaneous activity compared to the bladder dome and has at least two functions [4, 26, 41].

- Supplement closure of the uretero-vesical junction to prevent reflux of urine—the main mechanism being the oblique angle whereby the ureters penetrate the bladder wall to generate a non-return compression valve.
- Extend the bladder neck opening and provide rigidity to the base of the bladder to support the dome of the bladder during voiding.

Spontaneous contractions (Fig. 7.8) are accompanied by action potentials supported by Ca^{2+} influx into the myocyte *via* L-type channels, the opening of which are assisted by depolarisation from inward current *via* Ca^{2+}-activated Cl^- channels. Repolarisation is *via* K_{ATP} channels, rather than BK or SK channels. The ionic basic of electrical activity thus shows differences compared to that of detrusor. Connexin proteins (Cx43) label more extensively than in detrusor suggesting that spontaneous activity is supported by electrical communication between cells. However, electrical activity is independent of any in the detrusor and does not change during filling or voiding—valuable for spontaneous activity to assist in preventing reflux during filling.

Nervous control of the trigone also differs from detrusor, with both sympathetic (α-adrenergic) and parasympathetic components, as well as a non-adrenergic, non-cholinergic contractile and relaxatory input. Muscarinic and adrenergic receptor activation work together in a synergistic manner to augment contraction, with a rise of intracellular Ca^{2+} evoked through muscarinic receptor activation augmented by α-adrenergic receptor mediated Ca^{2+}-sensitisation of contractile proteins through a Rho-kinase pathway [27]. The balance between these synergistic pathways seems to alter with age. Relaxatory, nitergic nerves are also evident in the trigone, attenuated by inhibitors of nitric oxide synthases and mediated by a soluble guanylate cyclase pathway. There is coordination between the bladder and outflow tract, in part *via* intramural ganglia. Focal electrical stimulation of the bladder dome elicits signal spread to the urethra, that is inhibited by the ganglion blocker hexamethonium. These finding suggest that pre-ganglionic parasympathetic nerves may innervate both bladder and urethral intramural ganglia to facilitate coordinated activation of the two structures.

7.8.2 The Urethra

The concept of a single sphincter at the bladder base and proximal part of the urethra is a contentious subject. Several tissues combine to generate a region that controls the flow of urine from the bladder that is often called the internal urethral sphincter. By contrast, the incomplete ring of skeletal muscle that surrounds the more distal urethra forms a more recognisable sphincter mechanism (Sect. 7.8.3).

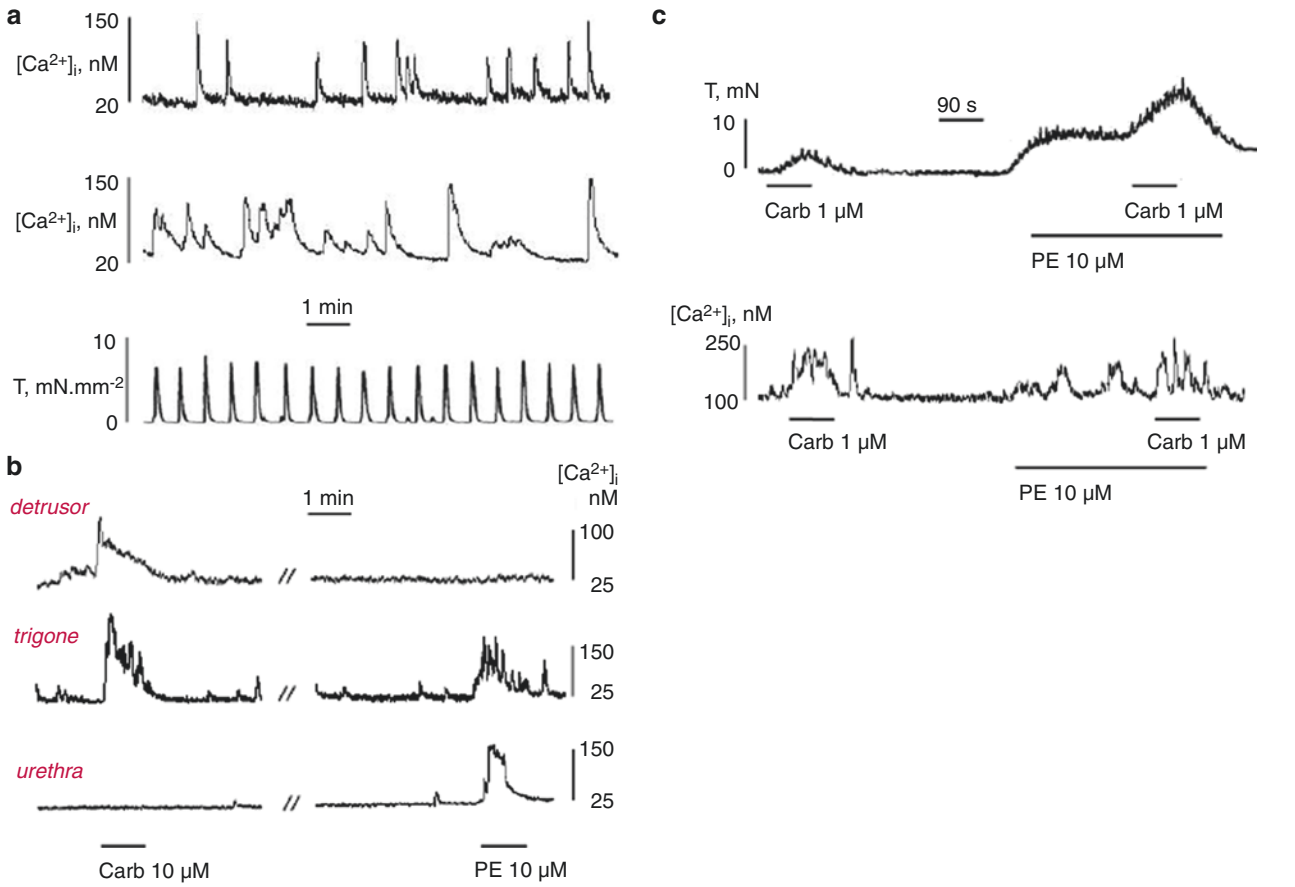

Fig. 7.8 Contractile characteristics of guinea-pig trigone smooth muscle. (**a**) Spontaneous activity. Upper two traces, different types of spontaneous intracellular Ca^{2+} transients in isolated myocytes. Lower trace: spontaneous contractions. (**b**) Differences in intracellular responses to a muscarinic agonist, carbachol (carb) and an α-agonist, phenylephrine (PE). Myocytes isolated from the bladder dome, trigone and urethra. (**c**) Synergistic actions of carbachol and phenylephrine in contractures (upper trace) and intracellular [Ca^{2+}] (lower trace). The contractile effect of carbachol was augmented by prior exposure to phenylephrine, however, the carbachol [Ca^{2+}] was not augmented by phenylephrine. It was shown that phenylephrine acts as a Ca^{2+} sensitiser of contractile proteins. Modified from Roosen et 2009

The internal sphincter has distinct longitudinal and circular muscular layers, a lamina propria and an epithelial lining. During the storage phase, the circular smooth muscle contracts to maintain a high fluid resistance in this region and the longitudinal smooth muscle relaxes to facilitate closure. This occurs through the release of noradrenaline from sympathetic terminals and activation of α1-adrenoceptors on the circular muscle and β3-adrenergic receptors on the longitudinal fibres. Alternatively, during the emptying phase, the circular fibres relax and the longitudinal fibres contract to lower fluid resistance and facilitate voiding. This is believed to occur in response to nitric oxide and acetylcholine released from parasympathetic nerve terminals that activate guanylate cyclase and stimulate M2/3 cholinergic receptors, respectively [42]. Urethral smooth muscle cells from both layers also display intrinsic contractile activity that promotes urethral tone and is contributed by similar activity in smooth muscle cells of the bladder base. An additional, often overlooked, factor that contributes to urethral resistance is blood flow through the substantial lamina propria. Decreased blood flow reduces intraurethral resistance and can be especially significant in atherosclerotic lesions of the bladder base [43].

Interstitial cells in the smooth muscle layers of the proximal urethra show physiological characteristics similar to interstitial cells of Cajal. It has been suggested that they communicate with the smooth muscle cells to promote intrinsic contractile activity. However, this mechanism has not been elucidated and urethral smooth muscle appears to maintain intrinsic activity in the absence of interstitial cells [44]. Another cell population that may modulate contractility of smooth muscle in the internal sphincter are neuroendocrine cells or paraneurons. These are found on the luminal surface of the urethra scattered between epithelial cells; they have microvilli that project into the lumen and can sense mechanical or chemical changes [45]. These cells also express transmitters such as chromogranin A, somatostatin and serotonin, which may be released in response to stimuli to regulate urethral tone.

7.8.3 The External Urethral Sphincter, the Rhabdosphincter

The skeletal muscle surrounding the urethra forms an incomplete ring in the middle to caudal third of the urethra, thicker on the ventral and lateral sides of the urethra and on the dorsal surface insert on to the vagina in women, or the perineal body in men. It is more defined in men, although in both there is a graded transition between skeletal and ureteric smooth muscle. In men extension of the rhabdosphincter also covers the distal part of the prostatic capsule by the prostatic apex. The efferent and afferent innervation of the rhabdosphincter, the neurochemistry of motor neurones in Onuf's nucleus and its supraspinal control is described elsewhere in the book and also in Thor and de Groat [46].

Rhabdosphincter muscles fibres are unusual as they do not attach directly to a skeletal structure so there is little active shortening on excitation. However, there is attachment to the levator ani (LA) muscles that will provide some rigid support. In females, the striated muscles are embedded in a matrix with many elastic fibrils and is continuous with a perineal membrane to allow connection with the pelvic ischia. In males this attachment to the LA is provided by a fairly rigid fascia that contains many smooth muscle cells. Electron microscopy reveals typical striated muscle sarcomeres with variation of mitochondrial number indicative of oxidative or glycolytic muscle fibres. Classical motor endplates are present with a 40–80 nm neuromuscular cleft. However, there is a lack of muscle spindles and Golgi tendon organs which implies that there are few spinal reflexes that optimise muscle function. The muscle fibres in the human rhabdosphincter are largely slow twitch, oxidative and non-fatigable as appropriate for muscle that requires contraction for long periods of time to generate a continence mechanism. In animals there is a greater proportion of fast twitch, glycolytic and fatigable fibres that may assist the function of producing urine in multiple, short squirts for marking purposes. It has been suggested that there is a dual somatic and autonomic innervation, but more recent evidence is that autonomic nerves merely pass *en route* to urethral smooth muscle [4].

Extracellular measurement of rhabdosphincter electrical (EMG) activity is a valuable tool to evaluate normal and abnormal function [47]. However, there is little information about the electrophysiological or contractile properties of rhabdosphincter muscle to help interpret clinical EMG recordings. With canine preparations motor nerves stimulation elicites twitch contractions at low frequencies (5 Hz) and fused tetani at higher frequencies (20 Hz). Twitch rise-time is slow, indicative of slow twitch fibres and responses were unaffected by atropine or phentolamine, consistent with somatic nerve stimulation. With guinea-pig preparations twitch characteristics were similar to those of a fast twitch muscle. No equivalent investigations are available from human samples. Electrophysiological measurements from cultured human and pig myoblasts show an action potential with an ionic basis similar to that from other skeletal muscle cells. However, T-type Ca^{2+} channel activity have also been recorded, that may reflect the fact that cells were dividing although it should also increase cell excitability. A human rhabdosphincter cell culture model retained a skeletal cell phenotype but is unclear if they represent a model of differentiated rhabdosphincter myocytes. However, its use as a cell replacement therapy for sphincter incompetence or stress urinary incontinence could add to the range of cell types used for this purpose. EMG recordings of complex repetitive discharges (myotonia-like activity) have been made from the rhabdosphincter of premenopausal women with urinary retention—Fowler's syndrome [48]. It was suggested to result from direct electrical coupling of muscle fibres without synaptic transmission (ephaptic transmission). This occurs in unphysiological conditions with high extracellular resistance and it is not known how this might apply to the rhabdosphincter.

Because the rhabdosphincter has a central role in maintaining continence there is interest in how its structure and function may change during ageing or other pathological conditions. In both humans and animals muscle mass is reduced with age that is uniform along the sphincter. Transurethral sonography shows a negative correlation between muscle thickness or urethral closure pressure and age. Stress incontinence in women is associated with reduced muscle volume, diminished sphincter function or muscle scarring [49]. In men rhabdosphincter damage post-prostatectomy is also associated with incontinence [50].

7.9 The Pelvic Floor Musculature

The pelvic floor lies at the base of the pelvis, supports pelvic visceral organs and may contribute to a continence mechanism, as the urethra and ano-rectum penetrate it. The innermost layer consists of the coccygeus muscles and the levator ani (LA). The LA itself has three components: the puborectalis; pubococcygeus and iliococcygeus muscles; the last two may also be called the pubocaudalis and iliocaudalis muscles in animals—Fig. 7.9. A more detailed description is found in Fry et al. [4]. In females, the LA muscles are innervated by the LA nerve that emerges from the S3–S5 segments: there is no evidence of pudendal nerve fibres. The course of the nerve differs between subjects; either along the inferior surface of the LA muscle after passing through the coccygeus muscle, or over the superior surfaces of the coccygeus and iliococcygeus muscles. This is important to reduce damage during surgical procedures and appreciate that LA and pudendal nerves at the ischial spine are only about 0.5 cm apart, so that pudendal nerve block would probably impact also on the LA nerve.

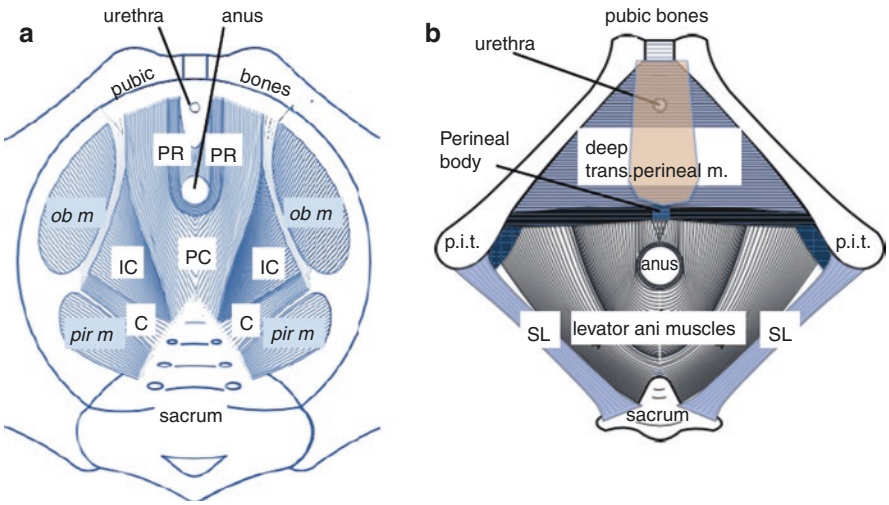

Fig. 7.9 The pelvic floor musculature from above (**a**) and below (**b**). (**a**) Diagram showing coccygeus (C), pubococcygeus (PC) and ileococcygeus (IC) muscles. The piriformis (pir m) and obturator internus (ob m) muscles are also shown. (**b**) Levator ani muscles in the centre and overlain by the deep transverse perineal muscle. The superficial transverse perineal muscle attaches to the perineal body. p.i.t, pelvic iscial tuberosities. Overlain (in orange) is the bulbospongiosus muscle

Large and small diameter motoneurones in the LA nerve may correspond to α-motoneurones and γ fibres that innervate LA muscle spindles and presumes that monosynaptic stretch reflexes can be evoked in the LA. Motoneurone processes also project to terminations of muscle spindle and Golgi tendon organs afferents, and also to Onuf's nucleus which implies coordination between the LA and urethral rhabdosphincter musculature. Female rabbits, as with humans, show complete cessation of external sphincter activity during micturition. The pubococcygeus is also quiet during voiding, and active during filling [51]. There is less work in males. With rats the pubococcygeus is innervated by a branch of the pelvic nerve that carries both sensory and motor nerves. The muscle is also attached to the urethral rhabdosphincter thus exerting a control over sphincter competence.

The LA musculature inserts onto bone, as do most other skeletal muscles, but also onto soft tissues such as the urethral and anal rhabdosphincters. In this regard muscle tendons are relatively rich in elastin to aid recovery of the original length after contraction [52]. Within the elastin are smooth muscle cells at the muscle/soft tissue interface and may act as viscous buffers.

Skeletal muscle fibres can be red, high oxidative capacity, non-fatigable (Type-I and -IIA) or white, low oxidative capacity, fatigable (Type-IIB). With muscle samples from women about two-thirds of fibres were Type-I, with the remainder mainly Type-IIB with no dependence on age, parity or presence of genitourinary prolapse and/or urinary incontinence [53], with similar observations from men. The preponderance of non-fatigable fibres may in part reflect the bipedal stance of humans with a greater need for continuous visceral organ support. There is very little work on characterisation of the contractile or electrophysiological properties of levator ani muscles. The small amount of work indicates properties similar to other muscle, but pathological changes—as in pelvic organ prolapse—remain to be studied.

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Pharmacology of the Lower Urinary Tract

8

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Abstract

The functions of the lower urinary tract, to store and periodically release urine, are dependent on the activity of smooth and striated muscles in the urinary bladder, urethra, and external urethral sphincter. This activity is in turn controlled by neural circuits in the brain, spinal cord, and peripheral ganglia. Various neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate, nitric oxide, and neuropeptides, both in the periphery and the central nervous system have been implicated in the neural regulation of the lower urinary tract. Injuries or diseases of the nervous system, as well as drugs and disorders of the peripheral organs, can produce lower urinary tract dysfunctions such as urinary frequency, urgency, pain and incontinence or inefficient voiding and urinary retention. This chapter will review recent advances in our understanding of the pharmacology in the control of lower urinary tract function and the targets for drug therapy.

8.1 Peripheral Nervous System

8.1.1 Muscarinic Mechanisms

8.1.1.1 Efferent Function and Detrusor Muscle

Excitation of parasympathetic postgangliomic nerves in the bladder releases acetylcholine (ACh) from nerve terminasl to induce detrusor muscle contractions during the voiding phase. ACh released form parasympathetic nerve terminals binds to muscarinic ACh receptors located on detrusor smooth muscles (Fig. 8.1).

There are at least five receptor subtypes based on molecular cloning and four different receptor subtypes based on pharmacology (M1–M5) [1–5]. In the human bladder, M1, M2, and M3 receptor subtypes have been found by receptor binding assays [6]; whereas all M1 to M5 receptor mRNAs are detected by reverse transcription–polymerase chain reaction assays [7, 8]. Although ligand receptor binding studies revealed that M2 receptors predominate, M3 receptors mediate cholinergic contractions [4, 5, 9–12]. (Fig. 8.2).

Stimulation of M3 receptors by acetylcholine leads to IP3 hydrolysis due to phospholipase C activation and then to the release of intracellular calcium and a smooth muscle contraction [10, 13]. The involvement of transmembrane flux of calcium ions through nifedipine-sensitive L-type Ca^{2+} channels has also been indicated in M3 receptor–mediated detrusor muscle contractions [7, 12, 14–17]. (Fig. 8.3). In addition, since the inhibition of Rho kinase reportedly suppresses carbachol-induced detrusor contractions in rats and humans, muscarinic receptor activation in detrusor smooth muscles is likely to stimulate the Rho kinase pathway, leading to a direct inhibition of myosin phosphatase that induces calcium sensitization to enhance the ability of the muscle to generate the same contractile force with lower levels of intracellular calcium [7, 15–17]. (Fig. 8.3).

It has also been proposed [5, 18] that coactivation of M2 receptors could enhance the response to M3 stimulation by (1) inhibition of adenylate cyclase, thereby suppressing sympathetically mediated depression of detrusor muscle; (2) inactivation of K^+ channels; or (3) activation of nonspecific cation channels. It has also been reported that the muscarinic receptor subtype–mediated detrusor contractions shift from M3 to M2 receptor subtype in certain pathologic conditions, such as obstructed or denervated hypertrophied bladders in rats [19–21], as well as in bladder muscle specimens from patients with neurogenic bladder dysfunction [22]. (Fig. 8.3).

Studies using mutant mice lacking the M3 receptor or the M2 and M3 receptors have demonstrated that this subtype plays key roles in salivary secretion, pupillary constriction, and detrusor contractions [23–25]. However, M3-mediated signals in digestive and reproductive organs are dispensable, probably because of redundant mecha-

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_8

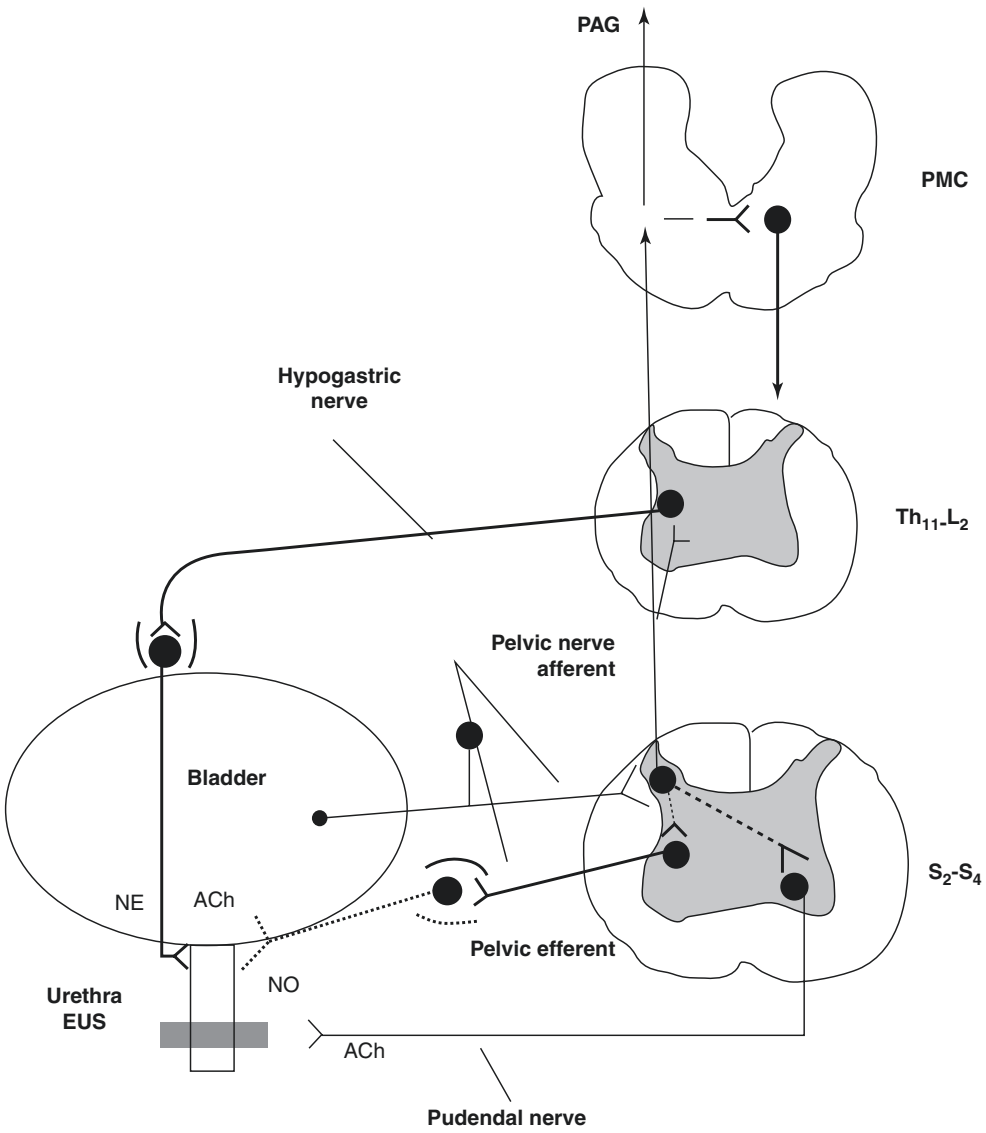

Fig. 8.1 Efferent pathways. Major preganglionic and postganglionic neural pathways from the spinal cord to the lower urinary tract: The sympathetic hypogastric nerve, emerging from the inferior mesenteric ganglion, stimulates urethral smooth muscle. The parasympathetic pelvic nerve, emerging from the pelvic ganglion, stimulates bladder detrusor muscle and inhibits urethral smooth muscle. The somatic pudendal nerve stimulates striated muscle of the EUS. Afferent pathways. Ascending afferent inputs from the spinal cord passes through neurons in the PAG to upper brain regions and the PMC. *ACh* acetylcholine, *NE* norepinephrine, *NO* nitric oxide, *S2-S4* sacral segments of the spinal cord, *T10-L2* thoracolumbar segments of the spinal cord; EUS, external urethral sphincter, *PMC* pontine micturition center, *PAG* periaqueductal gray

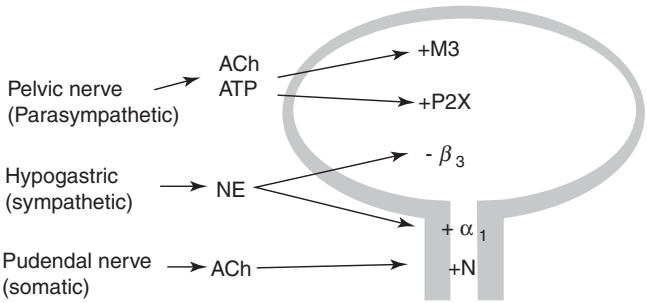

Fig. 8.2 Innervation of the lower urinary tract: The parasympathetic pelvic nerve stimulates the bladder detrusor muscle, mediated by muscarinic receptors (M3) being activated by ACh. The sympathetic hypogastric nerve stimulates urethral smooth muscle and inhibits bladder detrusor, mediated by α_1-adrenergic and β_3-adrenergic receptors, respectively. The somatic pudendal nerve stimulates striated muscle of the external urethral sphincter, mediated by ACh activating nicotinic (N) receptors. *ACh* acetylcholine, *NE* norepinephrine. Plus and minus signs indicate neural stimulation and inhibition, respectively

nisms through other muscarinic acetylcholine receptor subtypes or other mediators such as ATP [23]. In addition, it has also been found that male M3 knockout mice had the distended bladder and larger bladder capacity compared with females, indicating a considerable sex difference in the micturition mechanism [24, 25].

Muscarinic receptors are also located prejunctionally on cholinergic nerve terminals in the bladder [26–31]. Activation of M1 prejunctional receptors facilitates acetylcholine release [27, 28], whereas activation of M2–M4 receptors inhibits the release [12, 29, 30]. It has been proposed that inhibitory M2–M4 receptors are preferentially activated by autofeedback mechanisms during short periods of low-frequency nerve activity and thereby suppress cholinergic transmission during urine storage [27]. Conversely, M1 receptors are activated during more prolonged, high-frequency nerve firing that would occur during voiding and

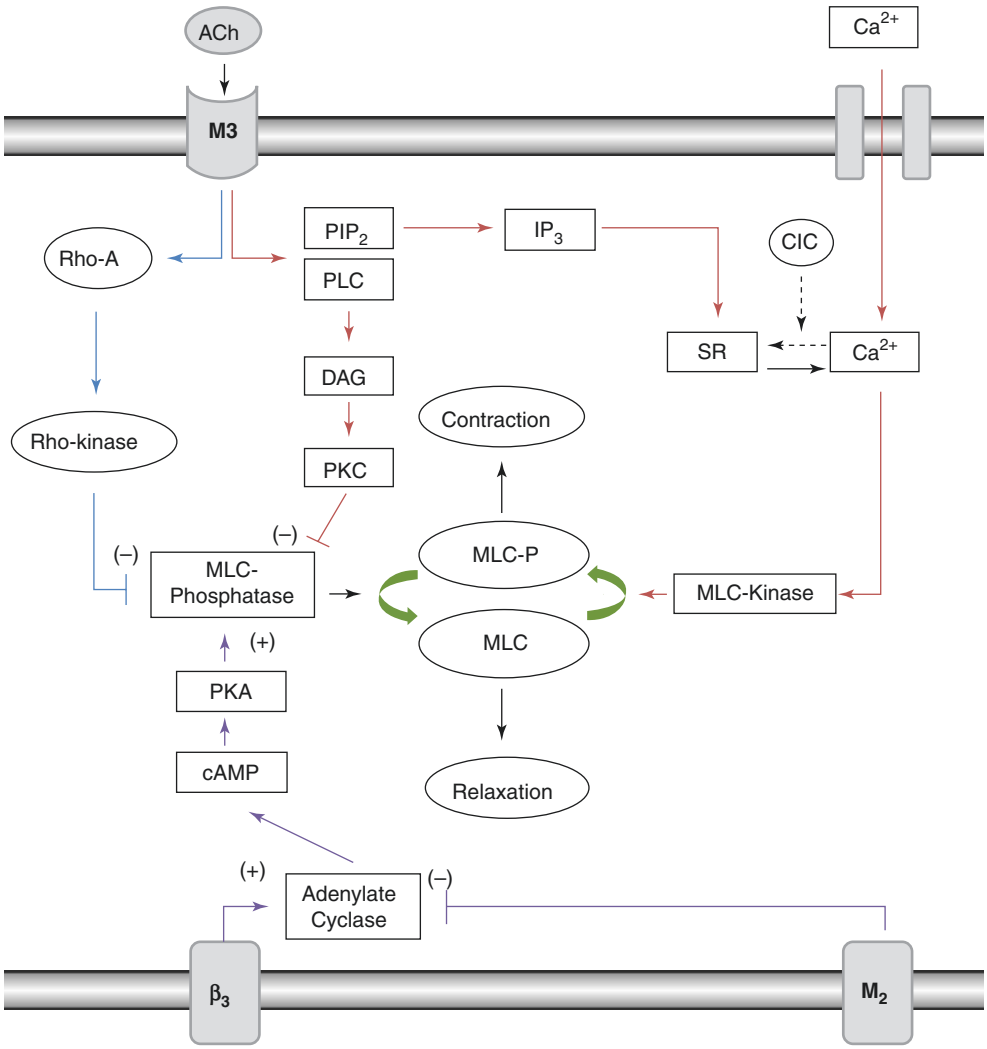

Fig. 8.3 Intracellular signaling pathways involved in activation and relaxation of detrusor contractions via M2 and M3 muscarinic and ß$_3$ adrenergic receptors, respectively. *ACh* acetylcholine, *PLC* phospholipase C, *DAG* diacylglycerol, *PKC* protein kinase C, *PKA* protein kinase A, *MLC* myosin light chain, *IP3* inositol trisphosphate, *PIP2* phosphatidylinositol 4,5-bisphosphate, *SR* sarcoplasmic reticulum, *CIC* calcium-induced calcium release. Intracellular Ca^{2+} release and Ca^{2+} influx contribute to contractions. Activation of M2 muscarinic receptors inhibits adenylate cyclase and reduces ß$_3$ adrenergic receptor mediated relaxation

thus participate in an amplification mechanism to promote complete bladder emptying. M1-mediated facilitation of transmitter release involves the activation of a phospholipase C–protein kinase C signaling cascade that appears to facilitate the opening of L-type Ca^{2+} channels that are necessary for prejunctional facilitation of acetylcholine release from parasympathetic nerve terminals [28, 32]. Inhibitory and facilitatory muscarinic receptors are also present in bladder parasympathetic ganglia, where they modulate nicotinic transmission [33].

8.1.1.2 Bladder Urothelium, Afferent Nerves and Interstitial Cells

Previous studies have shown that the bladder urothelium is a non-neuronal source of ACh release, which is induced by stretch of the urothelium by using vesicular storage and exocytosis mechanisms different from those in neuronal release of ACh [12]. The bladder urothelium of many species including humans also expressed multiple muscarinic receptors, with M2 andM3 receptors being most abundant at the mRNA and protein levels [34]. Activation of the muscarinic receptors in the urothelium releases substances (e.g., ATP) that modulate afferent nerves and smooth muscle activity [35, 36].

In bladder afferent pathways, it has been shown that dorsal root ganglion (DRG) neurons innervating the bladder express M2, M3 and M4 ACh receptors [37]. Systemic application of muscarinic receptor antagonists such as oxybutynin and darifenacin reportedly attenuates the afferent activity in response to bladder filling in rats [38, 39]. Also, intravesical administration of a muscarinic receptor agonist (oxotremorin-M) induces bladder overactivity, which is blocked by M2 receptor antagonists [40, 41]. These data suggest that activation of muscarinic receptors in the bladder has an excitatory effect on afferent nerve activity; however, it is not known due to the nature of in vivo studies if the facilitatory effects are mediated by direct interaction with muscarinic receptors expressed on afferent nerves or indirectly via the substances (e.g., ATP) released from the urothelium upon stimulation of urothelial muscarinic receptors.

Furthermore, muscarinic receptors such as M2 and M3 are also expressed in interstitial cells (IC) located in the suburothelial and detrusor layers (Fig. 8.4). Recent studies have revealed that bladder IC can modulate the bladder functions of filling and voiding in addition to sensory transduction by both excitatory and inhibitory mechanisms [42]. It has been shown that large Ca^{2+}-transients in detrusor IC induced by cholinergic receptor agonist (carbachol) are blocked by M3 antagonists with some sensitivity to M2 antagonists in mice and guinea pigs, raising the possibility that bladder IC can modulate the detrusor activity [43, 44].

Overall, the peripheral muscarinic receptor systems control lower urinary tract (LUT) function through multiple mechanisms that include not only direct smooth muscle activation, but also indirect ones via the urothelium and IC, which may help to explain in part the mechanism of action for muscarinic antagonists in reducing symptoms of bladder disorders such as overactive bladder (OAB).

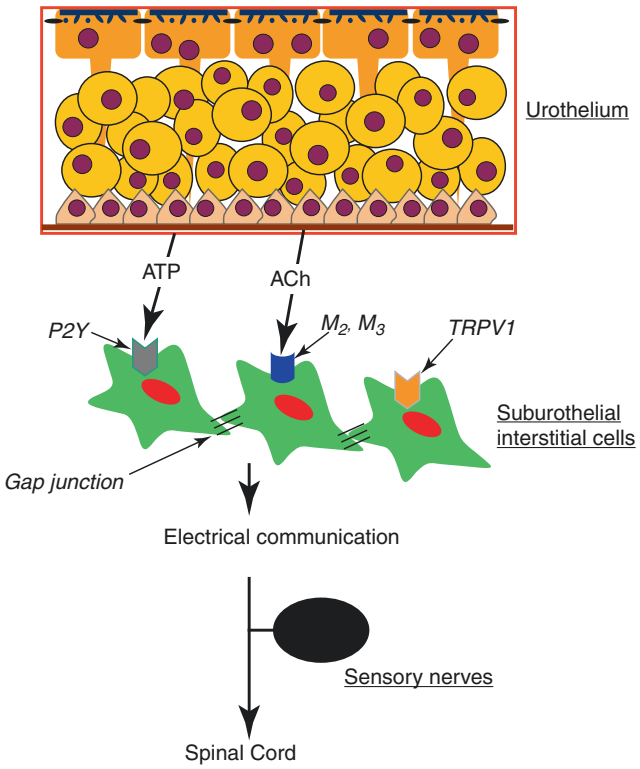

Fig. 8.4 Schematic representation of suburothelial interstitial cells (IC), which are also called myofibroblasts. Substances released from the basolateral surface during stretch, such as adenosine triphosphate (ATP) and acetylcholine (ACh), activate afferents in the suburothelial layer through the intermediation of suburothelially located interstitial cells, which express purinergic P2Y receptors, muscarinic M2 and M3 receptors or capsacin TRPV1 receptors, and are connected each other by gap junction proteins

8.1.2 Purinergic Mechanisms

8.1.2.1 Efferent Function and Detrusor Muscle

Purinergic contribution to parasympathetic stimulation has been shown to exist in a variety of species including rat, rabbit, and guinea pig [45–47]. However, there is less evidence for the contribution of purinergic neurotransmission in humans, at least in the normal micturition although it may play a role in pathologic conditions such as detrusor overactivity or bladder outlet obstruction [48–50].

ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G protein–coupled receptor family (P2Y) [51–53]. Seven P2X subtypes and eight P2Y subtypes have been identified. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that $P2X_1$ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder [54] (Fig. 8.2). Clusters of $P2X_1$ receptors were detected on rat bladder smooth muscle cells, some of which were closely related to nerve varicosities. Northern blotting and in situ hybridization revealed the presence of $P2X_1$ and $P2X_4$ mRNA in the bladder [55]. The predominant expression of $P2X_1$ receptors has also been confirmed in the human bladder [50, 56]. Investigators also found that the amount of $P2X_1$ receptors was increased in the obstructed bladder compared with the control bladder, suggesting upregulated purinergic mechanisms in the overactive bladder due to bladder outlet obstruction [50]. In addition, ATP also seems to act through P2Y receptors in the smooth muscle to suppress cholinergic and purinergic contractions [54, 57].

Purinergic nerves are also involved in the modulation of synaptic transmission in parasympathetic ganglia [58–61] because excitatory purinergic receptors in pelvic ganglia have been demonstrated in the cat [58], rabbit [59], and rat [60, 61].

8.1.3 Bladder Urothelium and Afferent Nerves

ATP is also released from urothelial cells during stretch and by chemical stimuli, and can activate a population of suburothelial bladder afferents expressing $P2X_2$ and $P2X_3$ receptors, signaling changes in bladder fullness and pain [62] (Fig. 8.5). Accordingly, $P2X_2$ or $P2X_3$ null mice exhibit bladder hyporeflexia, suggesting that this receptor as well as neural-epithelial interactions are essential for normal bladder function [63, 64] . However, recent studies reported that the $P2X_3$ receptor-mediated urothelial-afferent interaction is more important in bladder pathological conditions such as cystitis because, in mice, a lack of $P2X_2$ or $P2X_3$ receptors

did not show any changes in normal micturition, but attenuated bladder overactivity induced byipopolysaccharide (LPS) treatment in the bladder [65, 66]. ATP released from the urothelium or surrounding tissues may also play a role in the regulation of membrane trafficking. This is supported by studies in the urinary bladder in which urothelium-derived ATP release purportedly acts as a trigger for exocytosis—in part by autocrine activation of urothelial purinergic (P2X, P2Y) receptors [67]. These findings suggest a mechanism whereby urothelial cells sense or respond to ATP and thereby translate extracellular stimuli into functional processes (Fig. 8.5).

$P2X_3$ receptors that have been identified in small-diameter afferent neurons in DRG have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves [54]. Studies using patch clamp recordings in rats have also demonstrated that the majority (90%) of bladder afferent neurons projecting via pelvic nerves responded to α,β-methylene ATP and ATP with persistent currents, suggesting that bladder afferent pathways in the pelvic nerve express predominantly $P2X_{2/3}$ heteromeric receptors rather than $P2X_3$ homomeric receptors [68, 69]. Intravesical or intra-arterial administration of ATP or 2-methylthio-ATP activated bladder afferent fibers and enhanced reflex bladder activity [70–74]. Intra-arterial injection of ATP can also activate bladder afferent nerves [70], whereas suramin, an antagonist of certain types of ATP receptors (P2X purinergic receptors), given intravesically reduces by 50% the firing of bladder mechanoreceptors induced by bladder distention [75].

In addition, adenosine, which can be formed by the metabolism of ATP, can depress parasympathetic nerve-evoked bladder contractions by activating P1 inhibitory receptors in parasympathetic ganglia [76], in postganglionic nerve termi-

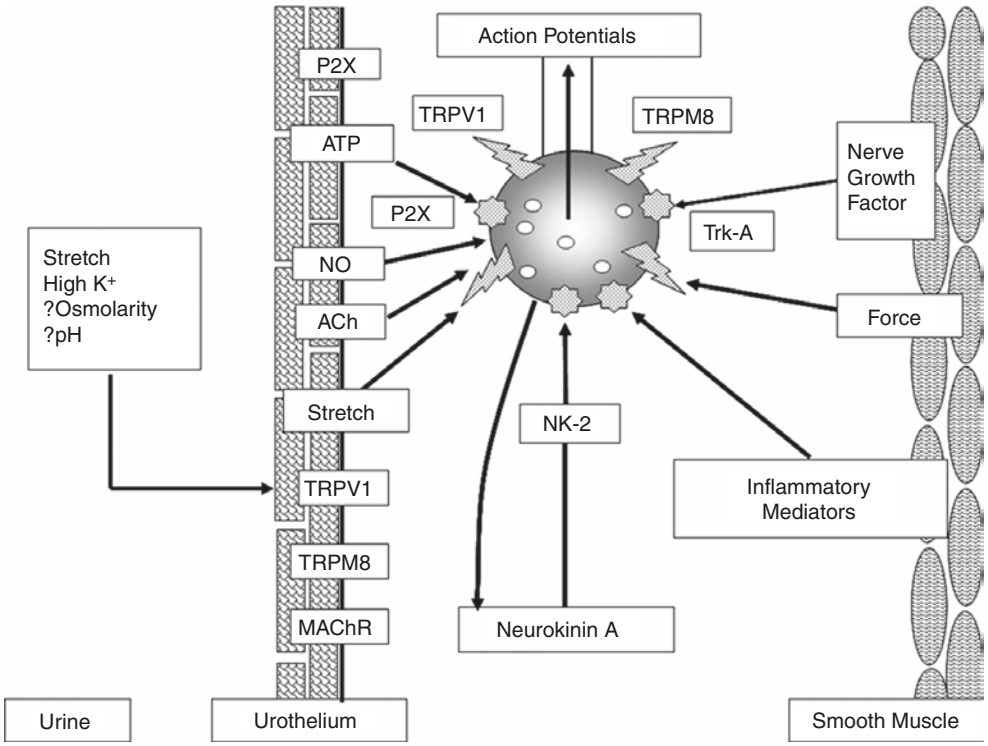

Fig. 8.5 Diagram showing: (1) receptors present in the urothelium (left side) and in sensory nerve endings in the bladder mucosa (center) and (2) putative chemical mediators that are released by the urothelium, nerves or smooth muscle (right side) that can modulate the excitability of sensory nerves. Urothelial cells and sensory nerves express common receptors (P2X, TRPV1 and TRPM8). Distension of the bladder activates stretch receptors and triggers the release of urothelial transmitters such as ATP, ACh and NO that may interact with adjacent nerves. Receptors in afferent nerves or the urothelium can respond to changes in pH, osmolality, high K^+ concentration, chemicals in the urine or inflammatory mediators released in the bladder wall. Neuropeptides (neurokinin A) released from sensory nerves in response to distension or chemical stimulation can act on neurokinin 2 (NK-2) autoreceptors to sensitize the mechanosensitive nerve endings. The smooth muscle can generate force which may influence some mucosal endings. Nerve growth factor released from muscle or urothelium can exert an acute and chronic influence on the excitability of sensory nerves via an action on Trk-A receptors. *ACh* acetylcholine, *MAChR* muscarinic acetylcholine receptor, *TRPV1* transient receptor potential vanilloid receptor 1 that are sensitive to capsaicin, *TRPM8* menthol/cold receptor, *NO* nitric oxide, *Trk-A* tropomyosin receptor kinase A receptor

nals, and in the bladder muscle [57, 64]. Adenosine P1 receptors have been further classified into a number of subtypes (i.e., A1, A2A, A2B, and A3) [77]. A study has demonstrated that adenosine reduces the force of nerve-mediated contractions by acting predominantly at presynaptic sites at the nerve-muscle junction through a subtype of an adenosine receptor (the A1 receptor in guinea pigs), although these actions of adenosine are less evident in human detrusor muscles [78]. Adenosine is also produced and released by the urothelium, and may contribute to the modulation of sensory afferent function and smooth muscle contraction [79]. A recent study also demonstrated that other purines including nicotinamide adenine dinucleotide (NAD+), ADP-ribose, and cADP-ribose content are released urothellially at different ratios during bladder filling although the functional role of these purines are not yet elucidated [80].

8.1.4 Adrenergic Mechanisms

8.1.4.1 β-Adrenergic

Stimulation of β_2- and β_3-adrenergic receptors that exist in the human detrusor results in the direct relaxation of the detrusor smooth muscle [81–84]. In addition, β-adrenergic–stimulated relaxation is mediated through the stimulation of adenylate cyclase and the accumulation of cyclic AMP (cAMP) [7, 13, 81]. Because β adrenoceptor–mediated relaxation of the human detrusor was not blocked by selective β_1 or β_2 adrenoceptor antagonists such as dobutamine and procaterol but was blocked by selective β_3 adrenoceptor antagonists, the relaxation induced by adrenergic stimulation of the human detrusor is mediated mainly through β_3 adrenoceptor activation [13, 85, 86]. A quantitative analysis by reverse transcription–polymerase chain reaction has also confirmed that the β_3-adrenergic receptor is the most highly expressed subtype among α and β adrenoceptor subtypes at the mRNA level in human bladders [87]. Thus, it has been considered that the major site of action of β_3-adrenoceptors is the detrusor muscle (Fig. 8.2); however, recent studies raised the possibility that other sites such as cholinergic nerve terminals and urothelium are involved in the β_3-adrenoceptor-mediated control of bladder activity. For example, β_3-adrenoceptors are abundantly located in ACh-containing nerve fibers in the mucosa and muscular layers of the human bladder [88]. Recent studies demonstrated that activation of prejunctional β_3-adrenoceptors can decrease ACh release from cholinergic nerve terminals via the adenosine-A1 receptor system, thereby leading to an inhibitory control of bladder activity during filling, in human and rat urinary bladders [89], β_3-Adrenoceptors are also shown to be expressed in the urothelium although the role of urothelial β_3-ARs in bladder relaxation has not yet to be fully elucidated [90, 91].

The β_3-receptor agonist mirabegron has been approved as a new treatment option for OAB with symptoms of urge incontinence [13, 92]. This agent has been shown to provide an alternative for patients with contraindications or intolerance to existing therapy, although combination therapy (mirabegron and the antimuscarinic solifenacin) has also been shown to be effective [93] The mechanism of action may be related to effects on multiple cell types including bladder afferent activity [94]. Findings in rodents have revealed that β_3- adrenoceptor stimulation with mirabegron increased bladder compliance and shortened the intervoid interval; this regulation may be a result of the effect at multiple sites including reduction of nonvoiding contractions and decreased afferent nerve activation [95, 96].

8.1.4.2 α-Adrenergic

Although α-adrenergic stimulation is not prominent in the normal bladder, under pathologic conditions such as detrusor overactivity associated with bladder outlet obstruction, the α-adrenergic receptor density, especially the α_{1D} receptor subtype, increases to such an extent that the norepinephrine-induced responses in the bladder are converted from relaxation to contraction [13]. In rats with bladder outlet obstruction, the proportion of α_{1D} receptor subtype in the total α_1 receptor mRNA in the bladder is increased to 70% from 25% in the normal rat bladders [97], and urinary frequency is suppressed by an inhibition of α_{1D} and α_{1A} receptors by tamsulosin whereas α_{1A} receptor suppression by 5-methyl-urapidil has no effects. Moreover, α_{1D} receptor knockout mice have larger bladder capacity and voided volumes than do their wild-type controls, supporting an important role of α_{1D} receptors in the control of bladder function [98]. However, in humans, there is the predominant expression of α_{1D} receptors already in the normal bladder [99], and the level of expression of α adrenoceptor mRNA, which is considerably low compared with β_3 adrenoceptors in normal bladders, was not increased in the bladder with outflow obstruction [87]. Thus, the contribution of α_{1D} receptors to detrusor overactivity observed in a variety of pathologic conditions including obstructive uropathy and incontinence still needs to be established [13].

α-Adrenergic mechanisms are more important in urethral function. Substantial pharmacologic and physiologic evidence indicates that urethral tone and intraurethral pressure are influenced by α-adrenergic receptors. The presence of α_1 and α_2 adrenoceptors has been shown in the urethra od various species including humans. Among α_1 adrenoceptors, the α_{1A} adrenoceptor is the major subtype expressed in urethral smooth muscles at the mRNA and protein levels [100, 101] (Figs. 8.1 and 8.2). Isolated human urethral smooth muscle contracts in response to α-adrenergic agonists [102–105]. It is also reported in the rabbit that the urethral contraction is mediated by the α_{1A} adrenoceptor subtype [101, 106]. Likewise, hypogastric nerve stimulation and α-adrenergic agonists produce a rise in intraurethral pressure, which is blocked by α_1-adrenergic antagonists [102, 107].

Conversely, α adrenergic receptor antagonists facilitate urine release in conditions of functionally increased urethral resistance, such as benign prostatic hyperplasia. In accordance with the α_{1A} adrenoceptor being the major subtype in the prostate and urethra, highly-selective α_{1A} adrenoceptor antagonists (e.g. silodosin) significantly improve lower urinary tract symptom (LUTS) scores in men with BPH [108]. In addition, α_1 adrenoceptor antagonists that contain α_{1D} adrenoceptor blocking activity also improve bladder-based symptoms in humans [109], suggesting that the α_{1D} adrenoceptors contribute to storage symptoms associated bladder outlet obstruction, which are potentially located at the bladder or the spinal cord [110].

α_2-Adrenergic antagonists increase the release of norepinephrine from urethral tissues through a presynaptic mechanism, but this does not affect the contractility of urethral smooth muscle in vitro [101, 105, 111]. The human urethra lacks postjunctional α_2-adrenergic receptors, although in vitro prejunctional activation of these receptors produces a feedback inhibition of norepinephrine release. Pharmacologic and electrophysiologic data suggest that adrenergic nerves influence excitatory cholinergic transmission in pelvic ganglia. It has been shown in the cat that hypogastric nerves inhibit excitatory cholinergic transmission in vesical ganglia by activation of α_2-adrenergic receptors [112].

8.1.5 Nitric Oxide

8.1.5.1 Efferent Function

Nitric oxide (NO) has been identified as a major inhibitory transmitter mediating relaxation of the urethral smooth muscle during micturition [81, 113–115] (Fig. 8.1). In the rat, NO is released by postganglionic nerves arising from neurons in the major pelvic ganglia [116]. These neurons contain nitric oxide synthase (NOS), the enzyme that synthesizes NO, as well as nicotinamide adenine dinucleotide phosphate–diaphorase, a marker for NOS [117]. Electrophysiologic studies in female rats showed that electrical stimulation of the lumbosacral (L6-S1) spinal roots elicits simultaneous bladder contractions and urethral relaxation [116]. The urethral relaxation was inhibited by NOS inhibitors, which did not alter the bladder responses. The inhibition was reversed by administration of L-arginine, a precursor of NO. The electrically evoked urethral relaxation was abolished by ganglionic blocking agents, indicating that it was mediated by stimulation of preganglionic parasympathetic axons in the lumbosacral roots.

NO-mediated smooth muscle relaxation is due to stimulation NO-sensitive guanylyl cyclase (NO-GC), resulting in increased production of intracellular cyclic guanosine monophosphate (cGMP). NO-GC is found in urethral smooth muscles, but not in bladder detrusor muscle; therefore, NO can induce urethral relaxation, but does not relax detrusor smooth muscle, indicating a minor role of NO-mediated relaxation mechanisms in the bladder, although NO-GC is expressed in vascular smooth muscle or interstitial cells in the bladder [118].

cGMP is inactivated by PDEs by hydrolytic cleavage of the phosphodiester bond. Therefore, the level of intracellular second messengers can be regulated by PDE isoenzymes [119, 120]. Because of their central role in regulating smooth muscle tone and the considerable variation of PDE isoenzymes among species and tissues, PDEs have become an attractive target for drug development.

8.1.5.2 Afferent Nerves and Urothelial Function

NO is also involved in controlling bladder afferent nerve activity. Inhibitors of NOS, given systemically or intrathecally, do not affect normal micturition in conscious or anesthetized rats. However, detrusor overactivity that accompanies irritation with turpentine, acetic acid or cyclophosphamide is ameliorated by spinal application of NOS inhibitors [121–123]. However, intravesically administered capsaicin induces detrusor overactivity that is not influenced by an intrathecally applied NOS inhibitor, although the behavioral effects of the irritation are reduced [124]. It is shown that NO is involved in mediating *N*-methyl-D-aspartate (NMDA) receptor–dependent effects but not those involving neurokinin 2 (NK2) receptors. Overall, the NO mechanism at the spinal level has an excitatory effect on the micturition reflex.

In contrast, NO seems to have an inhibitory effect in the bladder. NO can be released by the urothelium, particularly during inflammation [125]. The release of NO may be evoked by the calcium ionophore, norepinephrine, and capsaicin. Substance P also acts on receptors on urothelial cells to release NO. Bladder afferent nerves can also release NO because NOS expression is found in bladder afferent neurons and increased in chronic bladder inflammation or bladder outlet obstruction [126, 127]. Intravesical application of NO can suppress bladder overactivity due to cyclophosphamide-induced bladder irritation in rats [128]. Intravesical oxyhemoglobin, an NO scanvenger, also induces bladder overactivity as evidenced by reductions in bladder capacity and micturition volume, which is prevented by L-arginine or enhanced by the guanylate cyclase inhibitor in rats. Previous studies also showed that bladder overactivity induced by intravesical capsaicin instillation was enhanced by a NOS inhibitor (L-NAME) administered intravenously or intravesically and that these l-NAME-induced excitatory effects were significantly suppressed by desensitization of C-fiber afferent pathways by capsaicin pretreatment [129, 130]. Thus, NO released locally in the bladder can mediate inhibitory effects by modulation of bladder afferent activity [131].

8.1.5.3 PDE Inhibitor Treatment of Male LUTS

PDE5 inhibitors, which increases the tissue cGMP concentration by inhibiting degradation, has been approved and

shown to be effective for the treatment of male LUTS due to BPH [132]. It has been shown that the improvement of LUTS is associated with increased urinary flow, suggesting the urethral smooth muscle relaxation; however, the underlying mechanisms of drug efficacy seem to be multifactorial, which include the improvement of bladder ischemia due to vascular smooth muscle relaxation, inhibition of RhoA/Rho-kinase pathway activation in detrusor muscle and suppression of bladder/prostate afferent activity in addition to cGMP-mediated smooth muscle relaxation [133].

8.1.5.4 Possible Gender Difference in Cholinergic, Nitrergic and Adrenergic Innervation in the Urethra

A parasympathetic cholinergic excitatory input to the urethra has been identified in male but not in female rats [134, 135]. This was demonstrated by measuring intraurethral pressure during voiding after blockade of striated external urethral sphincter activity with a neuromuscular blocking agent. Under these conditions, urethral pressure increased during micturition in male rats. This urethral reflex was blocked by hexamethonium (a ganglionic blocking agent), markedly reduced by atropine, and increased by an NOS inhibitor. However, it was not changed by transection of sympathetic nerves or administration of an α_1-adrenergic blocking agent (prazosin). These results indicate that in male rats, parasympathetic nerve activity induces a predominant cholinergic muscarinic contraction of the urethra and a subordinate NO-mediated relaxation. These studies implicate possible gender differences in parasympathetic and especially nitrergic pathways in the human urethra. Furthermore, there also seems to be a gender difference in the α_1 adrenoceptor expression in urethra because α_{1A} adrenoceptor-induced contractions and α_{1A} adrenoceptor expression in the proximal urethra of male mice and marmoset monkeys are significantly greater than in the female counterpart [136].

8.1.6 Afferent Neuropeptides

Afferent neurons innervating the lower urinary tract exhibit immunoreactivity for various neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), leucine enkephalin, corticotropin releasing factor and vasoactive intestinal polypeptide (VIP) [137–142], as well as growth associated protein-43 (GAP43), nitric oxide synthase (NOS) [126], glutamic acid and aspartic acid [143]. These substances have been identified in many species and at one or more locations in the afferent pathways including: (1) afferent neurons in lumbosacral DRG, (2) afferent nerves in the peripheral organs and (3) afferent axons and terminals in the lumbosacral spinal cord [144–148]. The majority (>70%) of bladder DRG neurons in rats appear to contain multiple neuropeptides, CGRP, substance P or PACAP being the most common. In cats VIP is also contained in a large percentage of bladder DRG neurons [138]. Many of these peptides, which are contained in capsaicin-sensitive, C-fiber bladder afferents, are released in the bladder by noxious stimulation and contribute to inflammatory responses by triggering plasma extravasation, vasodilation, and alterations in bladder smooth muscle activity [140, 149, 150]. These peptides also function as transmitters at afferent terminals in the spinal cord.

8.1.6.1 Tachykinins

Tachykinins are a family of small peptides sharing a common C-terminal sequence Phe-Xaa-Gly-Leu-Met-NH2 whose main members are SP, neurokinin A, and neurokinin B. Tachykinins are found in both central and peripheral nervous systems. In the peripheral nerves, tachykinins are predominantly located in the terminals of nonmyelinated C fiber afferent pathways. The diverse biologic effects of the tachykinins are mediated through three receptors, designated NK1, NK2, and NK3, which belong to the superfamily of seven transmembrane–spanning G protein–coupled receptors [151]. Substance P is the most potent tachykinin for the NK1 receptor, whereas neurokinin A exhibits the highest affinity for the tachykinin NK2 receptor and neurokinin B for the tachykinin NK3 receptor. All receptor subtypes have been identified in the bladder in humans and animals such as rats, mice, and dogs [13, 152].

Tachykinins released from capsaicin-sensitive sensory C fibers in response to irritation in the bladder can act on (1) NK1 receptors in blood vessels to induce plasma extravasation and vasodilation, (2) NK2 receptors to stimulate bladder contractions, and (3) NK2 receptors on primary afferent terminals to increase the excitability during bladder filling or during bladder inflammation [81, 138, 148, 152, 153] (Fig. 8.5). It has also been demonstrated that activation of NK3 receptors on capsaicin-sensitive C-fiber afferents in the rat bladder can increase the excitability during bladder filling [154].

Intrathecal administration of NK1 antagonists (RP 67580 and CP 96345) or systemic application of centrally acting NK1 antagonists (GR 205171 and CP 99994) increased bladder capacity in normal rats and guinea pigs, respectively, without changing voiding pressure, whereas NK2, NK3, or peripherally acting NK1 antagonists were ineffective [155, 156]. Detrusor overactivity in rats induced by chemical cystitis, intravesical administration of capsaicin, or intravenous injection of L-dopa was also suppressed by intrathecal injection of NK1 antagonists [149, 157, 158]. Detrusor overactivity induced by capsaicin was reduced by an NK2 antagonist (SR 48965) that did not influence normal voiding [159]. In the anesthetized guinea pigs, TAK-637, an NK1 receptor antagonist, administered orally or intravenously, also increased the volume threshold for inducing micturition and

inhibited the micturition reflex induced by capsaicin applied topically to the bladder [160]. In a clinical study, an NK1 receptor antagonist, aprepitant, is also shown to effectively decrease the average daily number of micturitions and urgency episodes compared with placebo in women with idiopathic overactive bladder [161] although a later clinical study using another NK1 receptor antagonist showed that the reduction in the average daily number of micturitions was significantly greater compared with placebo; but not as good as the efficacy of tolterodine in patients with OAB [162]. These results indicate that sensory inputs to the spinal cord from non-nociceptive bladder afferents is mediated by tachykinins acting on NK1 receptors, whereas input from nociceptive afferents in the bladder can be mediated by NK1, NK2, and NK3 receptors. In addition, tachykinin NK3 receptor activation in the spinal cord can inhibit the micturition reflex through an activation of the spinal opioid mechanism [154]. Furthermore, autofeedback mechanisms may be important at afferent nerve terminals because sensory neurons obtained from rat DRG can be excited by NK2 agonists and inhibited by NK3 agonists through modulation of Ca2+ channel activity mediated by protein kinase C activation [163]. NK2 receptor activation also leads to PKC-induced phosphorylation of TRPV1 channels, resulting in an increase in capsaicin-evoked currents in rat DRG neurons [163, 164].

8.1.6.2 Other Neuropeptides

Other afferent neuropeptides have effects on the peripheral organs or the central reflex pathways controlling the lower urinary tract. However, the effects can vary in different species and at different sites in the lower urinary tract. CGRP applied exogenously or released from primary afferents relaxes smooth muscle and produces vasodilation. The effect of CGRP on bladder is prominent in the guinea pig and dog but is absent in the rat and human bladder [81]. VIP, which is contained in C-fiber afferents as well as in postganglionic neurons [112], inhibits spontaneous contractile activity in isolated bladder muscle from several species, including humans. However, VIP usually has little effect on bladder contractions induced by muscarinic receptor agonists or nerve stimulation [81]. In vivo studies in the cat revealed that VIP facilitates muscarinic but not nicotinic transmission in bladder parasympathetic ganglia and also depresses neurally evoked contractions of the bladder [30].

In the spinal cord, VIP-containing afferent pathways have been implicated in the recovery of bladder reflexes after spinal injury. In cats with chronic spinal injury, VIP immunoreactivity, which is a marker for C-fiber afferent terminals, is distributed over a wider area of the lateral dorsal horn, suggestive of afferent axonal sprouting after spinal injury [160, 165]. In addition, the effects of intrathecal administration of VIP are changed after spinal injury. In normal cats, VIP inhibits the micturition reflex; whereas in spinalized cats, VIP facilitates the micturition reflex, suggesting that the action of a putative C-fiber afferent transmitter may underlie the emergence of C-fiber bladder reflexes after spinal injury. In the normal rat, VIP and PACAP, another member of the secretin-glucagon-VIP peptide family, also facilitate the micturition reflex by actions on the spinal cord [158, 166, 167]. A study using PACAP null mice showed that PACAP gene disruption induces changes in bladder morphology, bladder function and somatic and visceral hypoalgesia [168]. In rats with spinal cord injury, increase in expression of PACAP-immunoreactivity in bladder DRG neurons and expansion of PACAP-IR afferent axons in the lumbosacral spinal cord are observed and intrathecal administration of PACAP6-38, a PAC1 PACAP receptor antagonist, reduces premicturition contractions during bladder filling and reduces maximal voiding pressure, suggesting that activation of PAC1 receptors by endogenous PACAP contributes to the micturition reflex and bladder overactivity in spinalized rats [169, 170]. Chemical inflammation of the rat bladder also increases PACAP expression in bladder afferent neurons [149, 171]. In addition, patch clamp studies in the neonatal rat spinal slice preparation also revealed that PACAP has a direct excitatory action on parasympathetic preganglionic neurons due in part to blockade of K^+ channels [172].

8.1.7 Prostanoids and Endothelins

8.1.7.1 Prostanoids

Prostanoids (prostaglandins and thromboxanes), which comprise a family of oxygenated metabolites of arachidonic acid via the enzymatic activity of cyclooxygenases 1 and 2, are manufactured throughout the lower urinary tract and have been implicated in bladder contractility, inflammatory responses, and neurotransmission. Biopsy specimens of human bladder mucosa contain prostaglandin (PG) I2, PGE2, PGF2α, and thromboxane A. The actions of prostanoids are mediated by specific receptors on cell membranes, which include the DP, EP, FP, IP, and TP receptors that preferentially respond to PGD2, PGE2, PGF2α, PGI2, and thromboxane A2, respectively. Furthermore, EP is subdivided into four subtypes: EP1, EP2, EP3, and EP4 [173, 174]. EP receptors are reportedly found in the urothelium, detrusor smooth muscle and intramural ganglia [175, 176]. In the guinea pig bladder, the major production of prostaglandins occurs in the urothelium and where production increases greatly with inflammation [177]. In mice PGE2 provokes ATP release from cultured urothelial cells, which express EP1 receptors; and bladder overactivity induced by intravesical application of PGE2 is prevented in EP1 receptor-knockout mice, suggesting the involvement of EP1 receptors in the PGE2-mediated urothelial-afferent interaction and bladder overactivity [178, 179]. Thus, EP1-selective antagonists may improve bladder storage function; however, the EP1 receptor antagonist ONO-8359 failed to

show the therapeutic efficacy compared with placebo for the treatment of patients with overactive bladder (OAB) [180].

The EP3 receptor is also involved in the modulation of bladder function in the normal condition as well as bladder overactivity induced by enhanced PGE2 production evoking DO because EP3 receptor null mice have a reduction in bladder overactivity in response to bladder PGE2 infusion and demonstrate a larger bladder capacity than wild type mice under the normal condition [181]. The EP4 receptor is also another candidate for the treatment of bladder overactivity because of the findings that; (1) intravenous application of an EP4 antagonist (AH23848) reduced bladder overactivity induced by cyclophosphamide without affecting normal micturition in rats [182], and (2) intravesical infusion of another EP4 antagonist (ONO-AE1-329) significantly decreased KCl-induced contraction of bladder strips and increased bladder capacity in rats with bladder outlet obstruction without changes in controls [176].

Despite that PGE2 can enhance the micturition reflex, clinical attempts to use prostaglandins to facilitate voiding have had mixed results. Intravesical PGE2 has been shown to enhance bladder emptying in women with urinary retention and patients with neurogenic voiding dysfunction [183–185]. Others have failed to find PGE2 useful to facilitate complete evacuation of the bladder [186, 187]. Intravesical PGE2 does produce urgency and involuntary bladder contractions [188]. However, more recently, the EP2 and EP3 receptor dual agonist (ONO-8055), which induces EP3-mediated detrusor contraction and EP2-mediated urethral relaxation, has been shown to improve inefficient voiding in animal models of detrusor underactivity induced by lumbar spinal canal stenosis (rat) [189] and hysterectomy (monkey) [119].

8.1.7.2 Endothelins

Endothelins (ETs), a family of 21–amino acid peptides originally isolated from bovine aortic endothelial cells, include ET-1, ET-2, and ET-3, which are encoded by separate genes and mediate a variety of biologic actions through two distinct G protein–coupled receptor subtypes, the endothelin-A (ET_A) and the endothelin-B (ET_B) receptor [190, 191]. The ET_A receptor subtype has a higher affinity for ET-1 and ET-2 than for ET-3; the ET_B receptor subtype binds all ETs with equal affinity [192]. ET-1, which is known to be primarily produced by human endothelial cells, can induce prolonged contractile responses in isolated urinary bladder muscle strips in various species [193, 194]. In humans and rabbits, ET-like immunoreactivity is identified in almost all cell types in the bladder, including bladder epithelium, vascular endothelium, detrusor and vascular smooth muscles, and fibroblasts; it plays a role in control of bladder smooth muscle tone, regulation of local blood flow, and bladder wall remodeling in pathologic conditions [195]. In a rabbit model of bladder outlet obstruction, ET-1 and ET_A receptor binding sites in detrusor smooth muscle and urothelium as well as ET_B receptor binding sites in detrusor smooth muscle were significantly increased [193, 196]. In addition, the endothelin-converting enzyme inhibitor WO-03028719, which suppresses ET-1 production, can improve voiding efficiency and suppress detrusor overactivity in a rat model of bladder outlet obstruction [197]. YM598, a selective ET_A receptor antagonist, also reduces detrusor overactivity in urethral obstructed rats [198]. These results suggest that the increase in ET-1 expression and ET receptors could be involved in detrusor hyperplasia and overactivity seen in patients with bladder outlet obstruction resulting from benign prostatic hyperplasia.

There is also evidence that ETs have a role in modulation of sensory function in the peripheral and central nervous system. The activation of ET_A receptors in capsaicin-sensitive C-fiber afferents in the bladder induces detrusor overactivity, whereas ET_A receptor activation in the spinal cord can inhibit the micturition reflex through activation of a spinal opioid mechanism in rats [199]. In spinal cord injured rats, the bladder ET-1 level was increased, and the application of ABT-627, an ET_A antagonist, suppresses C-fiber-mediated detrusor overactivity. Taken together, modulation of ET_A receptor activity in bladder afferent pathways or the spinal cord could be effective in treating bladder overactivity or painful conditions [200].

8.1.8 Serotonin

Serotonin (5-HT) has been found in neuroendocrine cells along the urethra and in the prostate [201]. More recently, these cells are characterized as serotonergic paraneurons in the female mouse urethra, which show the close proximity to putative C-fiber afferent nerve fibers positive for CGRP, substance P and TRPV1 [202]. Intraurethral perfusion of serotonin also induced excitation of urethral afferent neurons and increased pain sensitivity during urethral distention, suggesting that irritative symptoms such as the urethral syndrome may arise because of urethral serotonergic mechanisms. The close proximity of CGRP-immunoreactive nerve fibers and 5-HT-positive endocrine cells has also been demonstrated in the prostatic urethra of male rats [203].

5-HT also has several pharmacologic effects on mammalian urinary bladders, both in vitro and in vivo. Human and pig isolated detrusor muscles are known to contract in a concentration-dependent manner in response to 5-HT [204]. In human isolated urinary bladder, there was potentiation of the contractions induced by electrical field stimulation, mediated by the $5\text{-}HT_4$ receptor subtype [205, 206]. A similar response is present on guinea pig detrusor muscle through $5\text{-}HT_{2A}$ and $5\text{-}HT_4$ receptors, whereas in the rabbit and the rat, the receptors involved are the $5\text{-}HT_3$ and $5\text{-}HT_7$ subtypes, respectively [207]. Furthermore, contractile responses of bladder strips are reportedly enhanced and significantly reduced by a $5\text{-}HT_{2A}$ antagonist, in association of upregula-

tion of 5-HT_{2A} and 5-HT_{2B} receptors in detrusor muscle, in rats with bladder outlet obstruction [208, 209].

8.1.9 TRP Channels

The superfamily of TRP (transient receptor potential) channels expressed in mammals are subdivided into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin) groups, which are Ca^{2+} permeable cation channels and activated by physical (depolarization, hot/cold temperature, mechanical stress) or chemical (pH, osmolality) stimuli and binding to specific ligands (vanilloids. menthol). The available evidence suggests that TRP channels have a four-subunit combination, in either a homotetrameric or heterotetrameric complex, to form functional ion permeation complexes [210].

8.1.9.1 TRPV1

TRPV1, the most extensively studied TRP channel, is expressed on capsaicin-sensitive afferent pathways, predominantly C-fiber nociceptors, and responds to increases in temperature to the noxious range (>43°C) and by protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo. When it is activated, the channel opens, allowing an influx of Ca^{2+} and Na^{+} ions that depolarizes the nociceptive afferent terminals, initiating a nerve impulse that travels through afferent nerves into the central nervous system. Noxious temperature uses the same elements, which explains why the mouth feels hot when eating chili peppers [211]. In the lower urinary tract, TRPV1 is expressed in suburothelial afferent fibers, urothelium, detrusor smooth muscle and other non-neuronal cells such as suburothelial interstitial cells (Fig. 8.5). Studies using TRPV1 knock out mice provide the evidence showing that TRPV1 receptors are not essentially involved in conscious voiding, but have a role in afferent sensitization due to cystitis because bladder overactivity induced by chemical cystitis using cyclophosphamide or acrolein was not observed in TRPV1 knock-out mice [212–214]. In addition, TRPV1 expressed in the bladder urothelium may function as a stretch sensor because the release of ATP and NO from cultured urothelial cells during hypotonic stretch is reduced in TRPV1 knockout mice compared with the wild type [212].

In patients with spinal cord injury–induced detrusor overactivity, clinical response to intravesical therapy with RTX led to a marked decrease of nerve fibers positively stained for PGP9.5, a neuronal marker, and TRPV1. Six of 17 patients in this investigation showed a satisfactory clinical response to RTX treatment, with marked improvements on cystometry and other parameters [215]. Spinal-injury patients who did not respond to RTX showed no decrease in nerve fiber population, similar to controls. In addition, intravesical RTX administered to patients with idiopathic detrusor overactivity delayed or suppressed involuntary detrusor contractions during filling cystometry. The mean interval to the first involuntary contraction more than doubled vs. baseline at 30 and 90 days; mean maximal cystometric capacity increased; the mean number of episodes of urinary incontinence daily fell to fewer than one; and mean daily frequency also decreased significantly [216]. It has also been reported that C-fiber desensitization induced by intravesical application of high-dose capsaicin and resiniferatoxin (RTX) is effective for treating painful symptoms in IC patients [217, 218] although a prospective, randomized clinical trial using intravesical RTX application showed no effect in patients with IC [219].

In addition, targeting TRPV1 receptors using selective TRPV1 antagonists is being evaluated for the treatment of bladder dysfunction. A oral TRPV1 antagonist (GRC-6211), has been shown to decrease bladder overactivity and noxious bladder input in cystitis animal models [220] and bladder contraction frequency [221]. It has also shown that a selective TRPV1 antagonist (JTS-653) significantly suppressed the capsaicin-induced increase in afferent nerve discharge and reduced bladder overactivity induced by intravesical infusion of resiniferatoxin or acetic acid, without affecting normal micturition [222]. Furthermore, herpes simplex virus (HSV) vector-mediated gene therapy against TRPV1 receptors in the bladder and afferent pathways suppressed bladder overactivity and enhanced bladder pain sensitivity in rats with resiniferatoxin-induced bladder inflammation [223]. These results suggest the possibility of TRPV1 antagonists for the treatment of bladder pain/overactivity.

8.1.9.2 TRPM8

TRPM8 is a member of the temperature sensitive TRP channels, which responds to cold temperature less than 23°C. Pharmacological agents that evoke cool sensation such as menthol and ilicin can activate TRPM8. In sensory pathways, TRPM8 is expressed in DRG and trigeminal ganglion neurons that do not express TRPV1, isolectin-B4, or CGRP, which are usually markers of C-fiber afferents. Thus, it seems that TRPM8 is expressed in a subpopulation of thermoceptive and nociceptive afferents, which are different from the TRPV1 expressing subpopulation. In the human lower urinary tract, TRPM8 expression is found the prostate, the testes, scrotal skin, and bladder [224]. In addition, although in the study by Stein et al., expression in the human bladder was limited to the urothelium (Fig. 8.5), Mukerji et al. showed TRPM8 immunoreactivity in the bladder urothelium as well as in fine nerve fibers in the suburothelial layer and that the number of TRPM8 positive C-fibers in the bladder suburothelium is increased in patients with idiopathic detrusor overactivity [225]. In animal studies, activation of TRPM8 channels in the guinea pig bladder by intravesical application of menthol reduces volume threshold for micturition and increases sensitivity to bladder cooling [226] while a TRPM8 antagonist, AMTB, decreases bladder contraction frequency without affecting contraction ampli-

tude in cystometry as well as the visceromotor reflex of abdominal muscle in response to noxious urinary bladder distension in rats [227]. More recently, intravenous application of a selective TRPM8 antagonist (RQ-00203078) is shown to increase bladder capacity and voided volume and decrease nerve firing activity of mechanosensitive C-fiber afferents in the normal condition, and reduced bladder overactivity and increased afferent firing induced by intravesical menthol in rats [228]. In another study in rats, intravesical application of a TRPM8 antagonist (DFL23448) increases micturition intervals, micturition volume and bladder capacity in the normal condition and reduced PGE2-induced bladder overactivity [229]. Furthermore, TRPM8 expression in bladder afferent neurons is increased in rats with bladder outlet obstruction [230]. Therefore, TRPM8 in bladder afferent pathways and urothelium could be involved in modulation of sensory function of the lower urinary tract. In addition, TRPM8 channels expressed in the skin have been shown to be involved in cold stress-induced bladder overactivity because a TRPM8 channel antagonist (BCTC) inhibited bladder overactivity induced by menthol applied to the leg skin or by an exposure to low-temperature environment [231]. These results raise the possibility that the TRPM8 channel can be a therapeutic target for certain types of bladder overactivity.

8.1.9.3 TRPA1

TRPA1 is the only member of the Ankyrin TRP channel, and a receptor for several pungent chemicals that evoke pain such as allyl-isothiocyanate (the pungent compound in mustard oil), allicin (garlic), cinnamaldehyde (in cinnamon) and acrolein (the metabolite of cyclophosphamide). TRPA1 also functions as a receptor-operated channel that can be activated by growth factors or proinflammatory peptides such as bradykinin, which increases intracellular Ca^{2+} levels via G protein-coupled receptors. TRPA1 is expressed in sensory neurons, in which it is co-expressed with TRPV1, but not with TRPM8. Although TRPA1 can be activated by cold (<17°C) via an increase in intracellular Ca^{2+} concentration when expressed in heterologous systems, its role as a cold sensor in native peripheral sensory neurons including DRG cells remains uncertain. In mice, cooling does not evoke unspecific rises in Ca^{2+} concentration in DRG neurons while visceral sensory neurons in nodose ganglia exhibit a strong correlation between cold sensitivity and TRPA1 expression [232], suggesting that TRPA1 may contribute to cold transduction in visceral sensory neurons rather than somatic neurons [233]. In the bladder, TRPA1 is expressed in the urothelium, TRPV1 and CGRP-positive suburothelial afferent nerves and detrusor muscles in mice, rats and humans [234, 235]. TRPA1 receptor activation by intravesical application of hydrogen sulfide, allyl isothiocyanate and cinnamaldehyde induces frequent voiding as evidenced by a reduction in intercontraction intervals, which is suppressed by capsaicin-induced C-fiber desensitization in rats [235, 236]. Additionally, intravenous administration of a TRPA1 antagonist (HC-030031) reduced the single unit mechanosensitive afferent activity during bladder filling and prevented the increase in afferent activity during TRPA1 channel stimulation in rats [237]. Furthermore, TRPA1 mRNA expression in the bladder mucosa from male patients with lower urinary tract symptoms due to bladder outlet obstruction has shown to be significantly increased compared with control subjects [235]. In rats with spinal cord injury, intravenous administration of a TRPA1 antagonist (HC-030031) or intrathecal treatment with antisense oligodeoxynucleotide of TRPA1 receptors is effective in suppressing detrusor overactivity whereas the TRPA1 expression is increased in the bladder and L6-S1 dorsal root ganglia (DRG) in these animals [238]. Overall, TRPA1 channels expressed in the bladder urothelium and sensory pathways may have a role in sensory transduction in pathological conditions including overactive bladder.

8.1.9.4 TRPV4

TRPV4 is a member of vanilloid TRPV channels and a nonselective cation channel activated by mechanical pressure, osmolality (hypotonicity), moderate warmth (>27 °C) and chemical stimuli such as phorbol derivates. Its expression has been detected in urothelial cells and detrusor muscle, but not in the suburothelial layer, in the bladder of mice, rats and guinea pigs [239–243]. The TRPV4 agonist, 4α-phorbol 12,13-didecanoate, and hypotonic cell swelling promote Ca^{2+} influx and evokes ATP release in cultured urothelial cells from mice or rats [239, 240]. In cultured urothelial cells from TRPV4 knockout mice, the intracellular Ca^{2+} increase and ATP release in response to stretch stimulation were significantly attenuated compared to the wild type mice [244]. Cystometric experiments revealed that TRPV4 knockout mice exhibit a lower frequency of voiding contractions as well as a higher frequency of nonvoiding contractions [240] and that intravesical application of TRPV4 agonists induces bladder overactivity as evidenced by increased micturition pressure in rats [239] or reduced contraction frequency in mice [241]. In addition, intravesical application of a TRPV4 agonist (GSK1016790A) is shown to induce P2X receptor-mediated bladder overactivity by activation of mechanosensitive, capsaicin-insensitive C-fiber afferents in rats [245]. Furthermore, intravesical application of a TRPV4 antagonist (HC067047) reduced bladder overactivity observed after repeated variate stress, which is associated with increased urothelial TRPV4 expression [246]. These results suggest that urothelial TRPV4 channels act as an important molecule to enhance bladder activity, predominantly through activation of bladder afferent pathways via urothelially released ATP.

In addition to the functional role of urothleilal TRPV4 channels, recent studies suggest that TRPV4 channels in the forebrain is involved in the decision of early timing of voiding in mice [247] and that activation of TRPV4 channels in the detrusor muscle suppresses spontaneous contractions through activation of BK channels, which is likely to function as a self-limiting mechanism for reducing bladder contractility during bladder filling in guinea pigs [248]. The latter finding is in line with the observation in decerebrated TRPV4 null mice, which showed the increase of non-voiding contractions during bladder filling [247].

8.1.10 Cannabinoides

Cnnabinoid (CB) is the general term of bioactive substances contained in cannabis, and more than 60 kinds of CBs are found in cannabis [249, 250]. Of the more than 60 different CBs, tetrahydrocannabinol (THC), which is a major active ingredient of the drug marijuana, can induce mind-nerve reactions such as euphoria and relaxation, followed by drowsiness, sedation, and depression [249]. Effects of CBs are mediated of two types of G protein-coupled receptors; CB1 and CB2, which are expressed throughout the lower urinary tract including bladder urothelium, submucosal afferent nerves and detrusor muscle [251]. Pharmacological experiments using exogenous application of CB agonists revealed that activation of both CB1 and CB2 receptors increases threshold pressure and micturition intervals while minimally affecting voiding function, suggesting that CB receptor activation mainly inhibits the afferent limb of the micturition reflex [251]. At the spinal cord level, CB1 and CB2 receptor activation by intrathecal applications of their ligands is effective to reduce bladder pain sensitivity in animal models of cystitis [252, 253]. Furthermore, it has been shown that inflammatory changes in the bladder can be improved by CB2 receptor activation in rats with chemically-induced cystitis [254].

These data indicate that CB receptor modulation could be a new modality for the treatment of bladder overactivity and pain conditions. However, because the exocannbinoid therapy can induce the side effects in the central nervous system, modulation of the endocannabinoid system may be an alternative and attractive option. Endocannabinoids are endogenously generated substances that are degraded by two enzymes: fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [255]. While the latter is less investigated, the FAAH and its target endocannabinoid, anandamide, have been studied to elucidate their roles in the control of lower urinary tract function. Application of FAAH inhibitors such as URB937 or OEA reduces PGE2-induced firing of C-fiber afferents and frequent urination in normal rats [96, 256] and attenuates referred hyperalgesia in rats with experimental cystitis [257]. These results suggest that the endocannabinoid system could be a therapeutic target for OAB and hypersensitive bladder disorders such as interstitial cystitis/bladder pain syndrome (IC/BPS).

8.1.11 Botulinum Toxin

There has been increasing evidence for the therapeutic efficacy of botulinum neurotoxin (BoNT) for the treatment of various lower urinary tract dysfunctions [258–261].

Botulinum toxins act by inhibiting acetylcholine release at the presynaptic cholinergic nerve terminal, thereby inhibiting striated and smooth muscle contractions. The toxins are synthesized as single-chain polypeptides with a molecular weight of about 150 kD [262]. Initially, the parent chain is cleaved into its active dichain polypeptide form, consisting of a heavy chain (approximately 100 kD) connected by a disulfide bond to a light chain (approximately 50 kD) with an associated zinc atom [263]. Four steps are required for toxin-induced paralysis: binding of the toxin heavy chain to a receptor, synaptic vesicle protein 2 (SV2) on nerve terminals, internalization of the toxin within the nerve terminal, translocation of the light chain into the cytosol, and inhibition of neurotransmitter release. Vesicle docking requires the interaction of various cytoplasm, vesicle, and target membrane proteins (i.e., synaptosome-associated membrane receptor [SNARE] proteins), some of which are specifically targeted with clostridial neurotoxins. For example, BoNT-A cleaves the cytosolic translocation protein SNAP-25, thus preventing vesicle fusion with the plasma [260, 264].

Seven immunologically distinct neurotoxins are designated types A, B, C, D, E, F, and G. Clinically, the urologic community has used commercial preparations of BTX-A to treat patients with neurogenic and idiopathic detrusor overactivity [262, 265–270]. Although ACh release from bladder parasympathetic efferent terminals is the primary target of BoNT treatment, suppression of bladder afferent activity with BoNT treatment is also evident because the reduction of urgency symptom in patients with neurogenic and idiopathic detrusor overactivity is associated with reduced expression of the capsaicin receptor (TRPV1) and the ATP receptor ($P2X_3$) in C-fibers [271]. In addition, in basic research, botulinum toxins are shown to suppress not only efferent nerve activity by inhibition of the release of acetylcholine but also afferent nerve activity by release inhibition of neurotransmitters such as substance P and CGRP from sensory terminals [272, 273]. Incubation of rat bladder strips with the botulinum toxin A for 3 h *in vitro* also reportedly reduce detrusor contractions induced by electrical field stimulation or capsaicin application, suggesting the dual toxin effects on efferent and afferent nerve terminals [274], although an earlier study with a shorter toxin incubation time for 10 min showed the negative results in mice and guinea pigs [275].

There is also evidence that the toxin can reduce the release of ATP from urothelial cells in normal and spinalized rats [276–279]. Thus, the use of the toxins has been expanded to treat patients with neurogenic or non-neurogenic overactive bladder and even IC/BPS [258, 261, 280, 281].

8.2 Central Nervous System

8.2.1 Spinal Ascending and Descending Pathways

8.2.1.1 Glutamate

Intrathecal or intravenous administration of glutamatergic NMDA or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonists in urethane-anesthetized rats depressed reflex bladder contractions and electromyographic activity of the EUS in animals with an intact spinal cord as well as in animals with chronic spinal injury [282, 283]. Studies in rats also indicate that activation of bladder preganglionic neurons (PGN) by input from the pontine micturition center (PMC) can be blocked by inotropic glutamate receptor antagonists, suggesting that the descending pathways from the PMC utilize glutamate as a neurotransmitter [284]. These results indicate that spinal reflex pathways controlling bladder and sphincter function utilize NMDA and AMPA glutamatergic transmitter mechanisms (Figs. 8.6 and 8.7). In spinal cord-injured rats, external sphincter muscle activity was more sensitive than bladder reflexes to glutamatergic antagonists, raising the possibility that the two reflex pathways might have different glutamatergic receptors [285]. This was confirmed with in situ hybridization techniques, which revealed that sacral parasympathetic PGN in the rat express high mRNA levels of GluR-A and GluR-B AMPA receptor subunits and NR1 but not NR2 NMDA receptor subunits [286]. Conversely, motoneurons in the urethral sphincter nucleus express all four AMPA receptor subunits (GluR-A, -B, -C and -D) in conjunction with moderate amounts of NR2A and NR2B as well as high levels of NR1 receptor subunits. It seems likely that this difference in expression accounts for the different sensitivity of bladder and sphincter reflexes to glutamatergic antagonists.

Glutamate also plays a role as an excitatory transmitter in the afferent limb of the micturition reflex. C-fos expression induced in spinal interneurons by activation of bladder afferents is suppressed by the administration of both NMDA and non-NMDA glutamatergic receptor antagonists [287–289]. Additionally, the spinal glutamatergic pathway is shown to

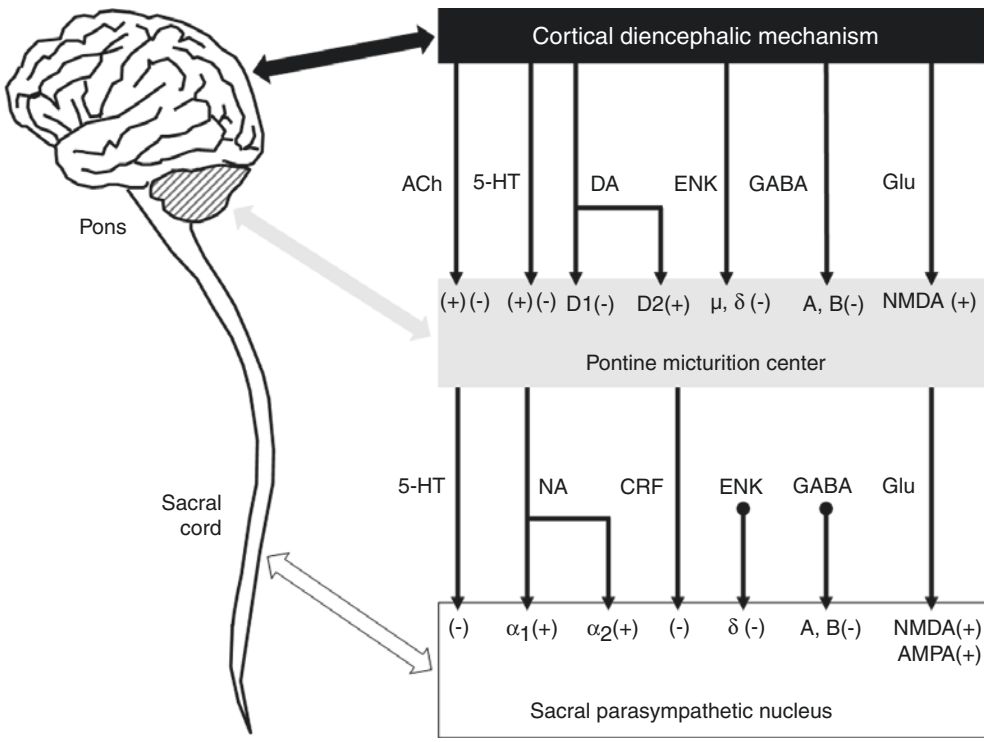

Fig. 8.6 Diagram of neurotransmitters at spinal and supraspinal sites. Glutamate is the major excitatory transmitter in control of the micturition reflex. Modulation of the micturition reflex in the spinal cord occurs by segmental interneuronal mechanisms (ENK, GABA) or by descending input from the brain (5-HT, NA, CRF). Modulation in the pontine micturition center can be activated in part by input from cortical–diencephalic areas. Facilitatory and inhibitory responses are indicated by plus and minus in parentheses, respectively. *ACh* acetylcholine, *CRF* corticotrophin releasing factor, *DA D1 and D2* dopamine receptors, *ENK* enkephalin, *GABA* gamma-aminobutyric acid receptors (A and B), *Glu* glutamate, *NA* norepinephrine, *μ* opioid receptors; *5-HT* 5-hydroxytryptamine

be involved in the external urethral sphincter (EUS) contraction reflex during sneezing via spinal AMPA receptor activation in rats. Intrathecal application of an AMPA receptor antagonist (NBQX) decreased the sneeze-induced urethral pressure responses without affecting urethral baseline pressure, and caused stress urinary incontinence during sneezing [290].

In contract to excitatory effects of glutamate via ionotropic glutamate receptors (NMDA and AMPA/kinate), activation metabotropic glutamatergic receptors (mGluRs) in the spinal cord has inhibitory effects on the descending limb of the micturition reflex because a group I/II mGluR agonist applied to the spinal cord at the lumbosacral level suppressed reflex bladder contractions as well as those induced by PMC stimulation in rats [291]. It has also been reported that mGluRs are involved in inhibition of the excitatory pathway to the external urethral sphincter (EUS) because a group I/II mGluR antagonist applied into the lumbosacral intrathecal space significantly facilitated the electromyogram activity of the EUS in rats [292].

In the synaptic transmission, glutamate released from presynaptic nerve terminals is cleared from synaptic clefts into presynaptic nerve terminals and adjacent astrocytes, via glutamate transporters. A previous study demonstrated that intrathecal application of a non-selective inhibitor of glutamate transporters, L-trans-pyrrolidine-2,4-dicarboxylic acid (L-trans-PDC) that increases endogenous glutamate concentration at nerve terminals, delayed the onset of micturition by increasing inter-micturition intervals and pressure thresholds in rats under urethane anesthesia [293].

8.2.1.2 Inhibitory Amino Acids (GABA, Glycine, Glycine Transporter)

Intrathecal injection of either $GABA_A$ or $GABA_B$ agonists increases bladder capacity and decreases voiding pressure and efficiency in normal rats [294, 295] and also suppress detrusor overactivity in rats with intravesical application of oxyhemoglobin, an NO scavenger [294] or spinal cord injury [296] (Figs. 8.6 and 8.7). In addition, intravenous or intrathecal application of a GABA re-uptake inhibitor (tiagabine)

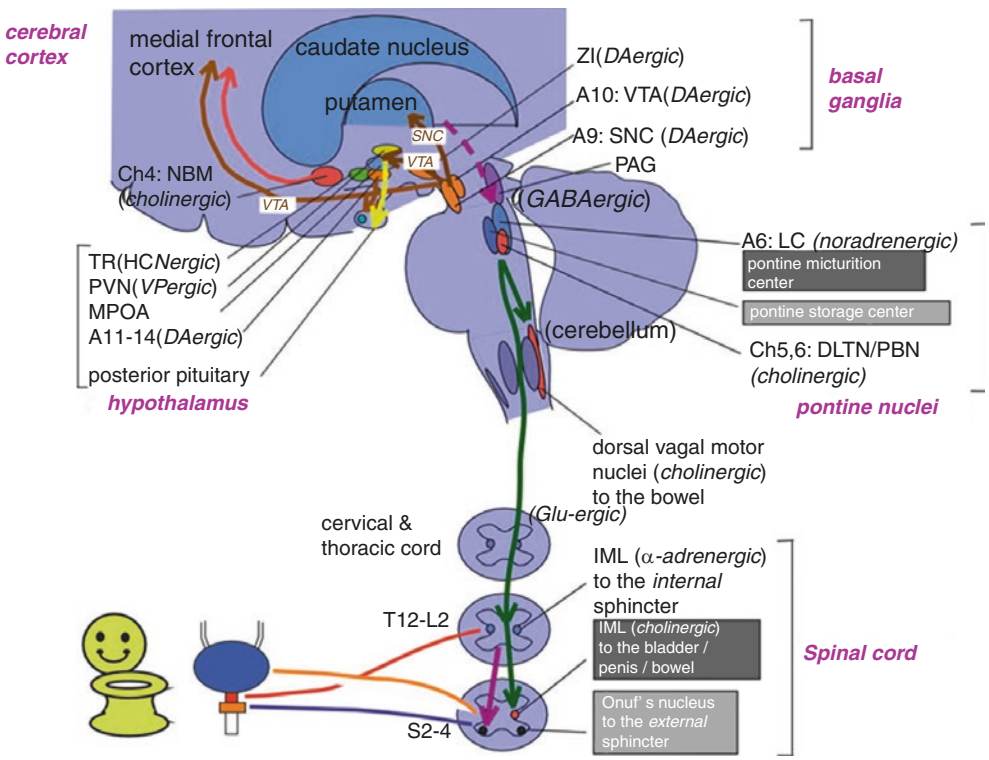

Fig. 8.7 Neural circuitry and neurotransmitteres relevant to micturition. The lower urinary tract consists of two major components, the bladder and the urethra. The bladder is mainly innervated by the parasympathetic pelvic nerve. The urethra is innervated by the sympathetic hypogastric nerve and somatic pudendal nerve, respectively. Urinary storage is dependent on the reflex arc of the sacral spinal cord. The storage reflex is thought to be tonically facilitated by the brain, particularly the pontine storage center. The storage function is thought to be further facilitated by the hypothalamus, cerebellum, basal ganglia, and frontal cortex. Central cholinergic fibers from the nucleus basalis Meynert (NBM, also called the Ch4 cell group) seem to facilitate urinary storage. Micturition is dependent on the reflex arc of the brainstem and spinal cord, which involves the midbrain periaqueductal gray (PAG) and the pontine micturition center (located in or adjacent to the locus coeruleus [LC]). The voiding function is thought to be initiated by the hypothalamus and prefrontal cortex, which overlap the storage-facilitating area. *PVN* paraventricular nucleus, *MPOA* medial preoptic area, *A* adrenergic/noradrenergic, *ZI* zona incerta, *VTA* ventral tegmental area, *SNC* substantia nigra pars compacta, *DLTN* dorsolateral tegmental nucleus, *PBN* parabrachial nucleus, *TR* tuberous region, *HCN* hypocretinergic, *DLTN* dorsolateral tegmental nucleus, *IML* IML cell column, *GABA* γ-aminobutyric acid, *T* thoracic, *L* lumbar, *S* sacral

that increases endogenous GABA concentrations reportedly inhibits normal micturition in rats [297]. In a small clinical study in three subjects, intrathecal administration of a $GABA_B$ receptor agonist (baclofen) increased the volume threshold for inducing the micturition reflex [298]. Intrathecally administered baclofen also produced phaclofen-sensitive inhibition of distention-evoked micturition in conscious rats that appears to be resistant to capsaicin (substance P depletion) and parachlorophenylalanine (5-hydroxytryptamine depletion) pretreatment [299]. Because baclofen also inhibits field stimulation–evoked release of calcitonin gene-related peptide from primary afferent terminals in dorsal horn slices, one possible site of action of suppression by baclofen is transmitter release from primary afferent terminals in the spinal cord.

Previous studies also showed that glycine, another inhibitory amino acid, acting on strychnine-sensitive receptors exerts an inhibitory effect on the micturition reflex pathway [300, 301] and is also involved in the inhibition of sphincter motoneurons during micturition [302]. Glycine and GABA inhibitory mechanisms have also been identified in the neonatal rat spinal cord in local intraneuronal inhibitory pathways projecting directly to the PGN [303]. Application of $GABA_A$ agonists to sacral parasympathetic PGN inhibits reflex firing, opens chloride channels, and hyperpolarizes the cells and b Baclofen, a $GABA_B$ agonist, suppresses Ca^{2+} channels in sacral preganglionic neurons in the rat [304].

In addition, some studies have revealed that the level of glycine in the spinal cord is decreased by approximately 50% in rats with detrusor overactivity induced by chronic spinal cord injury, compared with spinal intact rats [301, 303] and that dietary supplement of glycine can restore bladder function along with an increase in the serum level of glycine in spinal cord injured rats [304]. The level of glutamic acid decarboxylase (GAD), the GABA synthetic enzyme, is also reduced in the spinal cord and lumbosacral dorsal root ganglia in spinal cord–injured rats with detrusor overactivity and sphincter-detrusor dyssynergia, and both impaired functions are improved by intrathecal application of $GABA_A$ or $GABA_B$ receptor agonists [305, 306]. These results suggest that downregulation of spinal glycinergic and GABAergic mechanisms may contribute to the emergence of neurogenic detrusor overactivity associated with spinal cord injury.

The extracellular concentration of glycine at synapses is regulated by two types of Na^+/Cl^--dependent glycine transporters (GlyTs): GlyT1 and GlyT2 [307]. GlyT1 is widely distributed in the CNS and predominantly expressed in glial cells near both excitatory and inhibitory neurons, while GlyT2 is specifically distributed in the spinal cord, cerebellum, and brainstem, and localized in the presynaptic terminals of inhibitory glycinergic neurons [308]. A previous study reported that intrathecal application of a selective GlyT2 inhibitor, ALX-1393, but not a GlyT1 inhibitor, sarcosine, produced significant increases in inter-micturition intervals and pressure thresholds in rats with cyclophosphamide-induced cystitis [309], suggesting that inhibition of GlyT2 is a new approach to enhance the spinal glycinergic inhibitory mechanism controlling the micturition reflex.

8.2.1.3 Adrenergic

In the spinal cord, descending pathways form noradrenergic brainstem nuclei such as the locus coeruleus (LC) can mediate excitatory and inhibitory influences on the lower urinary tract via adrenoceptors (Figs. 8.6 and 8.7). In anesthetized cats, α_1-adrenoceptors were implicated in a bulbospinal noradrenergic excitatory pathway from the LC to the sacral parasympathetic outflow to bladder [310–312], although subsequent studies could not confirm these findings in conscious cats [313].

Experiments in conscious or anesthetized rats revealed that intrathecal administration of an α_1-adrenergic antagonist (doxazosin) decreased the amplitude of bladder contractions [314, 315]. The bladder inhibitory effect of intrathecal α_1-adrenergic antagonist was more prominent in animals with chronic outlet obstruction [314]. It was also found that intrathecal administration of doxazosin suppressed detrusor overactivity (unstable bladder contractions) in spontaneously hypertensive rats [124]. Although intrathecal injection of doxazosin suppressed the amplitude of reflex bladder contractions in anesthetized rats, it increased the frequency of isovolumetric contractions, indicating the presence of a tonic adrenergic inhibitory mechanism [316]. This was supported by the finding that phenylephrine, an α_1-adrenergic agonist, applied intrathecally, decreased the frequency of bladder contractions without changing contraction amplitude [316]. Overall, it appears that the spinal noradrenergic system has a modulatory role in the control of the micturition reflex and that efferent and afferent limbs of the micturition reflex receive excitatory and inhibitory input, respectively, from this system. Also, it has been reported that intrathecal injection of tamsulosin, an α_{1A}-selective adrenergic antagonist, or naftopidil, an selective $\alpha_{1A/D}$- adrenergic antagonist, transiently abolished isovolumetric rhythmic bladder contraction in normal rats [317] and that intrathecal injection of naftopidil prolonged the interval between voiding contractions and decreased the maximum voiding contraction pressure and the number of non-voiding contractions in spinal rats [318]. Intrathecal application of silodosin, a selective α_{1A} adrenergic antagonist, or naftopidil is also shown to increase bladder capacity in a rat model of cerebral infarction induced by middle cerebral occlusion [319]. These results suggest that α_{1A} and/or α_{1D} adrenoceptor subtypes are involved in the spinal excitatory mechanism controlling micturition in rats.

Evidence for a role of α_2 adrenoceptors in micturition is conflicting because both facilitatory and inhibitory roles of α_2-adrenoceptors have been documented [314, 316].

Atipamezole, an α_2-adrenergic antagonist given intrathecally, can increase micturition pressure in the conscious rat, implying that there is a tonic inhibitory adrenergic control [314]. However, yohimbine, an α_2-adrenergic antagonist, inhibits micturition in anesthetized rats [320]. In paraplegic patients, intrathecal injection of clonidine suppressed detrusor overactivity [321]. Conversely, in conscious spinal cats, clonidine, an α_2-adrenergic agonist, increased bladder pressures and facilitated voiding [322].

It is also known that locus coeruleus (LC) noradrenergic neurons are activated by visceral stimuli such as bladder and colon distension, and then modulate arousal and attention [323, 324]. Previous studies showed that the excitatory response of LC neurons to bladder distention was strongly affected by the state of anesthesia and that the response was accompanied by lightening of the anesthesia, indicative of arousal, detected by EEG recordings in rats [325]. Valentino et al. also reported that neurons containing corticotrophin-releasing factor in Barrinton's nucleus (i.e. the pontine micturition center) relay input from pelvic visceral afferents to the LC and may serve as a coordinating center of central and peripheral responses to pelvic visceral stimuli [324, 326].

Pharmacologic experiments showed that the bladder-to-sympathetic reflex pathway is also modulated by spinal noradrenergic mechanisms [316, 327, 328]. In the chloralose-anesthetized cat, prazosin or doxazosin, α_1-adrenergic antagonists, suppressed spontaneous firing [329] or the reflex discharge recorded on the hypogastric nerve in response to pelvic nerve afferent stimulation [327]. Administration of α_2-adrenergic agonists also suppresses reflex sympathetic activity [327]. These observations suggest that bulbospinal noradrenergic pathways provide a tonic α_1-excitatory control of the bladder-sympathetic reflex in the spinal cord. α_2-Adrenergic inhibitory mechanisms are not active under control conditions in anesthetized animals but can be up-regulated by elevating endogenous norepinephrine levels with an inhibitor (tomoxetine) of norepinephrine reuptake [327]. These results suggest that the lumbar sympathetic outflow is controlled by α_1-excitatory and α_2-inhibitory mechanisms.

The activation of urethral sphincter motoneurons by stimulation of bladder (pelvic nerve) or urethral/perineal (pudendal nerve) afferents is part of a continence-maintaining mechanism. These reflexes recorded as efferent discharges on the pudendal nerve in chloralose-anesthetized cats were suppressed by the α_1-adrenoceptor antagonist prazosin [327, 330], but not by the α_2 blocker idazoxan [327]. Using whole-cell patch clamp techniques in rat neonatal spinal cord slices, norepinephrine is shown to depolarize urethral sphincter motoneurons and evoke their action potentials, and these effects are blocked by prazosin, suggesting that there is a direct facilitatory mechanism increasing urethral sphincter motoneuron excitability by norepinephrine via α_1-adrenoceptors [331].

Conversely, clonidine, an α_2-adrenoceptor agonist, suppressed the reflex in anesthetized cats [332]. The norepinephrine uptake blocker tomoxetine produced a slight inhibition alone and only a slightly greater inhibition after prazosin. However, it greatly facilitated the reflex when given after idazoxan [327]. These data indicate the existence of α_2-adrenoceptor--mediated inhibitory and α_1 adrenoceptor--mediated tonic facilitation of sphincter function and that the α_2 adrenoceptor--dependent inhibitory mechanism is the dominant adrenergic modulator of the pudendal nerve reflex [333]. These α_1 and α_2 adrenoceptor--mediated facilitatory and inhibitory mechanisms, respectively, also contribute to the urethral continence reflex that prevents stress urinary incontinence because previous studies using a norepinephrine reuptake inhibitor nisoxetine or a norepinephrine/serotonin reuptake inhibitor, duloxetine, induces α_1-adrenoceptor activation in the lumbosacral spinal cord to enhance reflex contractions of the external urethral sphincter during sneezing [334, 335] and that α_2 adrenergic antagonists, yohimbine or idazoxan, enhances the duloxetine-induced urethral sphincter contraction during sneezing or abdominal compression in rats [336, 337].

8.2.1.4 Serotonergic

Neurons containing 5-HT in the raphe nucleus of the caudal brain stem send projections to the dorsal horn, as well as to the autonomic and sphincter motor nuclei in the lumbosacral spinal cord (Fig. 8.6). In cats, activation of raphe neurons or 5-HT receptors in the spinal cord inhibits reflex bladder contractions and firing of the sacral efferent pathways to the bladder [338–341] and also inhibits firing of spinal dorsal horn neurons elicited by stimulation of pelvic nerve afferents [342]. Extracellualar recordings of neuronal activity in the raphe nucleus in response to storage/voiding cycles under the isovolumetric condition have revealed that the most common (~50%) were tonic storage neurons that exhibited increased firing at an interval between reflex bladder contractions in cats [341].

In rats, the administration of m-chlorophenylpiperazine (mCPP), which is an agonist for 5-$HT_{2A/C}$ receptors, suppressed efferent activity on bladder nerves and reflex bladder contractions [343]. These effects were blocked by mesulergine, a 5-HT_2 receptor antagonist [343, 344]. Intrathecal administration of methysergide, a 5-$HT_{1/2}$ antagonist, or zatosetron, a 5-HT_3 antagonist, decreased the micturition volume threshold in cats [345], implying that descending serotonergic pathways tonically depress the afferent limb of the micturition reflex through $5HT_2$ and/or $5HT_3$ receptors.

The role of 5-HT_1 receptors in bladder activity seems different in cats and rats. In cats, administration of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), a 5-HT1A receptor agonist increased bladder capacity in chloralose anesthetized cats, in which the bladder was irritated with

acetic acid, but had only moderate effects on bladder activity in the absence of irritation [346]. The drug also had a facilitatory effect on activity of the external urethral sphincter. 8-OH-DPAT also inhibited reflex bladder activity in awake or chloralose-anesthetized, chronic spinal cord-injured cats, but did not alter the somato-bladder excitatory reflex induced in spinal cats by tactile stimulation of the perigenital region [347]. The effects of 8-OH-DPAT were blocked by WAY 100635, a 5-HT_{1A} receptor antagonist, which alone had no effect. These results indicate that 8-OH-DPAT acts in the spinal cord to inhibit the micturition reflex triggered by C-fiber bladder afferent axons and has much less effect on the spino-bulbo-spinal reflex elicited by Aδ-afferents.

In contrast, 8-OH-DPAT administered intrathecally facilitated bladder activity in both normal and spinal cord-injured rats but not in rats in which bladder afferents were damaged by treatment with capsaicin at birth [299]. Conversely, administration of the 5-HT_{1A} receptor antagonist WAY 100635, which increases the firing rate of raphe neurons by blocking 5-HT_{1A} inhibitory autoreceptors, inhibits reflex bladder contractions in rats [348]. The inhibition is antagonized by pretreatment with mesulergine, a 5-HT_2 receptor antagonist, indicating that 5-HT_2 receptors are involved in descending raphe/spinal inhibitory mechanisms [348]. Similar inhibitory effects of another 5-HT_{1A} receptor antagonist, NAD-299, on the micturition reflex have been reported in rats [349].

When the effects of intrathecal administration of WAY 100635 on the ascending and descending limbs of the micturition reflex pathway were examined in anesthetized rats, WAY 100635 depressed bladder contractions evoked by electrical stimulation of the pontine micturition center, but did not alter the evoked field potentials in the region of during electrical stimulation of afferent axons in the pelvic nerve, indicating that the drug suppresses the pathway from the brainstem to the spinal cord but does not alter the afferent pathway from the bladder to the pontine micturition center [350, 351]. Thus, micturition in the rat is facilitated by stimulation of $5HT_1$ inhibitory autoreceptors, whereas in the cat $5HT_1$ receptor activation appears to act primarily through postsynaptic mechanisms to promote urine storage by enhancing sphincter activity and suppressing bladder activity [352].

The sympathetic autonomic nuclei as well as the sphincter motor nuclei also receive a serotonergic input from the raphe nucleus [333, 345, 353]. Serotonergic activity mediated via 5-HT_2 and 5-HT_3 receptors enhances urine storage by facilitating sphincter reflexes in cats [345, 354]. Another study in rats also reported that activation of $5HT_{2C}$ receptors enhances the urethral closure reflex induced by pudendal nerve-mediated urethral striated muscle contraction during sneezing at the spinal level whereas $5HT_{1A}$ receptors inhibit it because intrathecally applied 8-OH-DPAT (a $5HT_{1A}$ agonist) decreases urethral contractile responses during sneezing and that mCPP (a $5HT_{2B/2C}$ agonist) increases them, and the effects of 8-OH-DPAT and mCPP are antagonized by intrathecal applications of WAY-100635, a selective $5HT_{1A}$ antagonist, and RS-102221, a selective $5HT_{2C}$ antagonist, respectively [355].

Duloxetine, a combined norepinephrine/serotonin reuptake inhibitor has been shown, in a bladder-irritated cat model, to increase the neural activity of both the urethral sphincter and the bladder [333, 356]. Duloxetine appears to have effects on both the bladder and the sphincter has been proposed as a treatment for both stress and urge incontinence [333, 357]. Duloxetine increases the neural activity to the EUS via 5-HT_2 receptors and α_1 adrenoceptors and decreases bladder activity via 5-HT_1 receptors in the spinal cord [333]. Clinical trials have also shown the efficacy of duloxetine for the treatment of stress urinary incontinence, and the drug has been approved in Europe and is already available in several countries [358] although it was withdrawn from the FDA approval process in the US by the manufacturer.

8.2.1.5 Acetylcholine

Muscarinic acetylcholine (mACh) receptors have an inhibitory effect on the micturition reflex in the spinal cord. In the rat, intrathecal application of an ACh receptor agonist, oxotremorine-M, or a cholinesterase inhibitor, neostigmine, increases bladder capacity and pressure thresholds, and these effects are atropine-sensitive, indicating the mACh receptor-mediated inhibitory action in the spinal cord [359–361]. Since intrathecal application of atropine by itself has no effects on the micturition reflex in normal rats, but decreases inter-micturition intervals in rats with cyclophosphamide-induced cystitis, the endogenous mACh mechanism for the inhibitory modulation of micturition, which is not tonically active in the normal condition, might be up-regulated after bladder inflammation [361]. Nicotinic receptors are also involved in the control of voiding function since intrathecal application of nicotine have an facilitatory effect on the micturition reflex in the rat [362].

Spinal mAChR also modulate the urethral continence reflex that prevents stress urinary incontinence since a cholinesterase inhibitor, neostigmine, administered intrathecally reduces the urethral closure reflex induced by pudendal nerve-mediated urethral striated muscle contraction during sneezing. The neostigmine-induced decrease in sneeze-induced urethral responses was reversed by pretreatment with atropine (nonselective mACh antagonist), methoctramine (M2 receptor antagonist) or 4-DAMP (M3 receptor antagonist), but not with pirenzepine (M1 receptor antagonist), tropicamide (M4 receptor antagonist), or mecamylamine (nicotinic receptor antagonist), suggesting the involvement of M2 and M3 mACh in muscarinic receptor-mediated modulation of urethral function [363].

8.2.1.6 Opioid Peptides

Opioid peptides have an inhibitory action on reflex pathways in the spinal cord. In the cat spinal cord, inhibition of reflex bladder activity is mediated by μ receptors whereas inhibition of sphincter activity is mediated by κ receptors [165, 328, 340]. In the rat, both μ and δ receptors mediate bladder inhibition [328, 364, 365]. The spinal opioid inhibitory system can also be activated by tachykinins via NK3 receptors [366] and by endothelins via endothelin A receptors to inhibit the micturition reflex [199].

Opioid receptors also seem to be involved in pudendal or tibial nerve neuromodualtion, which has been shown to be effective for the treatment of overactive bladder symptoms, because naloxone, an opioid receptor antagonist, reverses the increasing effect of pudendal or tibial nerve stimulation on bladder capacity during intravesical saline infusion or bladder overactivity induced by intravesical acetic acid infusion, respectively, in cats [366–369]. However, the site of action for opioid receptor activation during neuromodulation may not be limited in the spinal cord as naloxone was administered systemically in these studies.

8.2.2 Pontine Micturition Center and Supraspinal Pathways

8.2.2.1 Glutamate

Glutamic acid also has a role in excitatory transmission at supraspinal sites in the micturition reflex pathway (Fig. 8.6). A recent study has confirmed that the majority of corticotrophin-releasing factor (CRF)-positive neurons in the PMC, which send axons to the lumbosacral spinal cord, are glutamatergic cells positive for vesicular glutamate transporters [370]. Exogenous L-glutamate or its analogue injected at sites such as PMC or parabrachial nucleus in the brain stem of supracollicular decerebrate or chloralose anesthetized cats where electrical stimulation evoke bladder contractions [371], elicits voiding when the bladder is partially filled or increased frequency and amplitude of rhythmic bladder contractions when the bladder is filled above the micturition threshold volume and maintained under isovolumetric conditions [339, 372]. On the other hand, injections of glutamic acid at some sites in the PMC elicits inhibition of isovolumetric contractions or initial excitation followed by inhibition [373].

Administration of glutamatergic agonists into the region of the PMC in rats also elicits voiding or increases frequency and amplitude of bladder contractions [373, 374], whereas injection of agonists in the brain of rats and cats at other sites known to have inhibitory functions in micturition elicits inhibitory effects [339, 375–378]. Intracerebroventricular injection of AMPA or NMDA receptor antagonists blocks reflex bladder contractions in anesthetized rats, indicating that glutamatergic transmission in the brain is essential for voiding function [283].

In rat brain slices patch clamp recordings from pre-parasympathetic output (PPO) and pre-sympathetic output (PSO) neurons projecting, respectively, to the sacral parasympathetic and thoraco-lumbar sympathetic intermediolateral nuclei revealed that spontaneous EPSCs recorded after blocking GABAergic and glycinergic inhibitory receptors with bicuculline and strychnine were blocked by the AMPA glutamatergic receptor antagonist CNQX. This indicates that the neurons receive excitatory inputs from glutamatergic neurons located in the slice [378]. Blocking AMPA and NMDA ionotropic glutamate receptors also decreased the spontaneous firing of PSO neurons but paradoxically increased the firing of PPO neurons indicating that the latter neurons receive a tonic inhibitory input triggered by a glutamatergic mechanism. This is consistent with the observation mentioned above that injections of glutamate at some sites in the cat PMC unexpectedly inhibited reflex bladder activity [368].

A previous study also showed that a non-selective inhibitor of glutamate transporters, L-trans-PDC, administered into the lateral ventricle increased inter-micturition intervals and pressure thresholds in anesthetized rats, suggesting that activation of the overall glutamatergic system at the supraspinal site has an inhibitory effect on micturition, possibly via activation of glutamate-mediated inhibitory pathways [291].

8.2.2.2 Acetylcholine

Excitatory and inhibitory cholinergic influences on the micturition pathway have been identified at the supraspinal level using various techniques (Fig. 8.6). In the rat brain, muscarinic receptor-mediated cholinergic mechanisms may be involved in both inhibitory and facilitatory modulation of the micturition reflex [359, 379, 380], and the muscarinic inhibitory mechanism seems to involve an activation of M1 muscarinic receptors [379] and protein kinase C [381]. One site of action can be localized to the midbrain-pons region because cholinergic agonists are effective after supracollicular decerebration in rats [382]. In the brain stem, microinjection of acetylcholine to the PMC in cats increased or decreased the threshold volume for inducing a reflex contraction of the bladder [165, 383]. These effects were blocked by atropine, indicating a role of muscarinic receptors. Nicotinic receptors are also involved in the control of voiding function since nicotinic receptor agonists, epibatidine or nicotine, injected into the lateral ventricle have an inhibitory effect on the micturition reflex in the rat [362, 384]. A decreased volume threshold and increased micturition pressure were detected after administration of bethanechol, a muscarinic agonist, into the central circulation of the cross-perfused dog [385].

8.2.2.3 GABA and Glycine

GABA has been implicated as an inhibitory transmitter at supraspinal sites where it can act on both $GABA_A$ and $GABA_B$ receptors [165, 316, 328, 340, 386] (Figs. 8.6 and 8.7). As mentioned in an earlier section of this paper, injection of $GABA_A$ receptor agonists, into the PMC of decerebrate cats or into the PAG of rats suppresses reflex bladder activity and increases the volume threshold for inducing micturition [372]. These effects are reversed by bicuculline, a $GABA_A$ receptor antagonist; and bicuculline alone stimulates bladder activity and lowers the volume threshold for micturition, indicating that the micturition reflex pathway in the PMC and PAG is tonically inhibited by a GABAergic mechanism. Intracerebroventricular administration of melatonin increases bladder capacity in rats; and this effect is blocked by bicuculline indicating that melatonin activates a GABAergic inhibitory mechanism in the brain [387]. Intracerebroventricular injection of baclofen, a $GABA_B$ agonist, suppresses distention-evoked micturition in urethane-anesthetized rats but unexpectedly this effect is not blocked by phaclofen, a $GABA_B$ receptor antagonist [316, 328].

Patch clamp recordings in rat brain slices showed that blocking $GABA_A$ receptors with bicuculline increases the excitability of both pre-parasympathetic output (PPO) and pre-sympathetic output (PSO) neurons in the PMC, which are labeled by injecting fluorescent tracers into the intermediolateral region of the spinal cord at T13-L1 and S1-S2 levels, respectively, while blocking glycine receptors with strychnine increases the firing of only PPO neurons [388]. Blocking ionotropic glutamatergic receptors which increases firing of PPO neurons in untreated slices does change firing in the presence of strychnine, indicating that glutamatergic excitatory transmission generates the tonic glycinergic inhibitory input to PPO neurons.

8.2.2.4 Dopamine

In the central nervous system, dopaminergic pathways exert inhibitory and facilitatory effects on the micturition reflex through D1-like (D1 or D5 subtypes) and D2-like (D2, D3, or D4 subtypes) dopaminergic receptors, respectively [389–397] (Figs. 8.6 and 8.7). In anesthetized cats, activation of dopaminergic neurons in the substantia nigra inhibits reflex bladder contractions via D1-like receptors [391]. In awake rats a D1 dopaminergic antagonist (SCH 23390) facilitates the micturition reflex whereas a D1 agonist (SKF 38393) does not alter reflex bladder contractions, suggesting that D1 receptor--mediated suppression of bladder activity is tonically active in the normal awake state [396]. Conversely, activation of central D2-like dopaminergic receptors with quinpirole or bromocriptine facilitates the micturition reflex pathway in rats, cats, and monkeys [390, 392, 394, 395, 398]. D2-like receptor-mediated facilitation of the micturition reflex may involve actions on spinal cord as well as actions on the brain stem because microinjection of dopamine to the PMC reduced bladder capacity and facilitated the micturition reflex in cats [340].

It is also known in cats that neurons in the substantia nigra pars compacta and the ventral tegmental area, which are the major dopamine-containing nuclei in the midbrain, respond to the storage/micturition cycles of isovolumetric cystometry [399] and that dopamine levels in the striatum, where nigrostiatal dopaminergic nerves terminate, increase during the storage phase of the micturition cycle [400]. Thus, central dopaminergic pathways appear to be involved in the control of the bladder function through actions on multiple receptors at different sites in the brain.

Activation of D2-like receptors at a supraspinal site suppresses the activity of the striated sphincter muscle and reduces intraurethral pressure; whereas inhibition of dopamine D1- or D2-like receptors has a minimal effect on urethral function in anesthetized rats, suggesting the dopaminergic control of urethral function is minimally active in the normal condition [401].

Parkinson's disease (PD) is a degenerative disorder of central nervous system caused by the insufficient formation and action of dopamine, which is produced in the pathways from the substantia nigra to the striatum in the mid-brain. Clinical studies have demonstrated that patients with PD often have lower urinary tract symptoms such as nocturia, increased urinary frequency and urinary incontinence with he reported incidence ranging between 27–63.9% across different studies [402]. The most common finding in the urodynamic study is detrusor overactivity (DO) shown by uninhibited contractions during bladder filling [402]. In monkeys, disruption of nigrostriatal dopaminergic pathways induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produces PD-like motor symptoms accompanied by bladder overactivity shown by frequent urination with reduced voided volume [389, 392, 402]. A rat model of PD induced by a unilateral 6-hydroxydopamine injection into the substantia nigra exhibits a similar type of bladder overactivity [394, 403]. In these animal models, bladder overactivity was suppressed by enhancement of D1-like receptors with SKF 38393 or pergolide, suggesting that bladder overactivity in PD is primarily induced by disruption of D1-like dopamine receptor-mediated inhibition of the micturition reflex [392, 394, 398] (Fig. 8.8). In addition, in a rat model of PD, bladder overactivity was suppressed by an adenosine A2A receptor antagonist, ZM241385, suggesting that enhanced activity of the adenosine A2A system in the brain contribute to bladder overactivity associated with PD [403]. The adenosine A2A receptor-expressing neural pathways are very likely located downstream of D1 receptor expressing pathways in the control of micturition

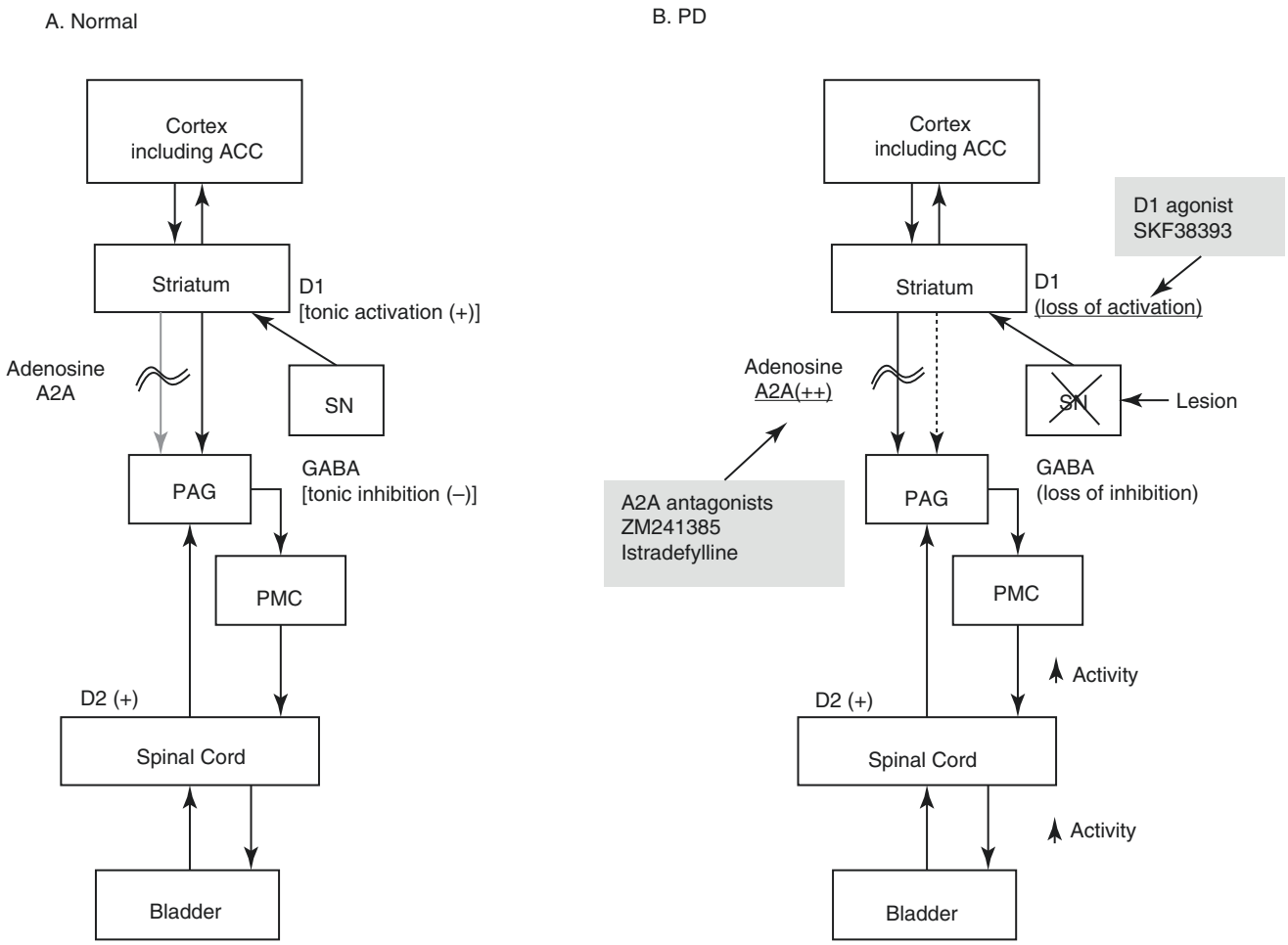

Fig. 8.8 A hypothetical diagram demonstrates working model of bladder dysfunction in Parkinson's disease (PD). This figure was adopted from ref. 61, and modified. Micturition reflex is controlled by spinobulbospinal pathways through PAG in midbrain and PMC in brainstem. This neural circuit is under control of higher centers including ACC and other cortex regions. A, under normal conditions tonic inhibition from ACC suppress micturition reflex. Tonic firing (+) of dopaminergic neurons in SN activates dopamine D1 receptors expressed on GABAergic inhibitory neurons in the striatum to induce tonic GABAergic inhibition (−) of the micturition reflex at the level of PAG. At the same time, D1 receptor stimulation suppresses the activity of adenosinergic neurons, which exert an excitatory effect on micturition via adenosine A2A receptors (+). B. In PD, dopaminergic neurons in the SN are lost (lesion), leading to the loss of dopamine D1 receptors activation [D1 (loss of activation)], which results in reduced activation inhibitory GABAergic neurons in the striatum [GABA (loss of inhibition)]. At the same time, reduced D1 receptor stimulation enhances the adenosinergic mechanism to stimulate adenosine A2A receptors [Adenosine A2A (++)], leading to facilitation of the spinobulbospinal pathway controlling the micturition reflex pathway. Administration of dopamine D1 receptor agonist (SKF38393) can restore the GABAergic nerve activity and suppress A2A receptor-mediated activation to reduce bladder overactivity in PD. Also, administration of adenosine A2A antagonists (ZM241385 or Istradefylline) can suppress A2A receptor-mediated activation of the micturition reflex to reduce bladder overactivity in PD. Dopamine D2 receptors [D2 (+)] expressed in the spinal cord enhances the micturition reflex. *ACC* anterior cingulate cortex, *GABA* gamma-aminobutyric acid, *PAG* periaqueductal gray, *PMC* pontine micturition center, *SN* substantia nigra pars compacta

because inhibition of bladder activity by D1 receptor activation can induce the partial suppression of adenosine A2A receptor-mediated excitatory mechanisms in the rat model of PD [403] (Fig. 8.8). To support this assumption, a recent open-labeled clinical study reported that treatment with istradefylline, a selective adenosine A2A receptor antagonist, for 12 weeks significantly improved lower urinary tract symptoms in 13 male PD patients although a larger-sized, placebo-controlled randomized study is needed to confirm the results [404].

8.2.2.5 Serotonin

The serotonergic system (5-HT) in the supraspinal site seems to also contribute to the modulation of the micturition reflex. A rat model of depression induced by clomipramine administration, which depletes the brain 5-HT concertation, exhibits frequent urination with bladder overactivity that is improved by a 5HT reuptake inhibitor (fluoxetine) [384]. These results suggest that the central 5-HT system exerts the inhibitory effect on micturition. More recently, increased concertation of 5-HT in the prefrontal cortex after fluoxetine

treatment has an inhibitory effect on the micturition reflex, which is blocked by a 5-HT_{1A} receptor antagonists in rats [405]. Because the prefrontal cortex is shown to be one of the major brain sites involved in the voluntary control of micturition in human brain imaging studies [406], it is likely that the brain 5-HT system is involved in the modulation of the prefrontal cortex activity to exert the inhibitory effects on micturition.

In contrast, the brain 5-HT system can be excitatory to induce bladder overactivity in the psychological stress condition. Recent studies demonstrated that bladder overactivity induced by intracerebroventricular (i.c.v.) application of bombesin, a stress-related neuropeptide, is suppressed by pretreatment with a 5-HT synthesis inhibitor (p-chlorophenylalanine) or i.c.v. application of a 5-HT_7 receptor antagonist (SB269970) [407, 408]. These results suggest that the 5-HT_7 receptor-mediated serotonergic mechanism may contribute to the emergence of bladder overactivity in the psychological stress condition.

8.2.2.6 Opioid Peptides

Intracerebroventricularly administered morphine suppresses isovolumic bladder contractions in rats and cats, and this effect is blocked by naloxone [364, 365, 409, 410] (Fig. 8.6). Naloxone administered intracerebroventricularly also reversed the effects of systemically administered morphine. Naloxone administered alone intracerebroventricularly or injected directly into the PMC facilitates the micturition reflex, indicating that micturition is tonically inhibited by a supraspinal opioid mechanism [410, 411]. Both μ and δ opioid receptors mediate inhibitory effects that are blocked by naloxone [372, 410]. In addition, activation of μ and δ1, but not δ2 opioid receptors in the brain increases bladder capacity in both normal rats and rats with cerebral infarction that exhibit frequent voiding; however, κ receptor activation increases bladder capacity only in rats with cerebral infarction [412]. In rat brain slices application of a specific μ opioid receptor agonist (DAMGO) suppresses the firing of pre-parasympathetic output (PPO) and pre-sympathetic output (PSO) neurons in the PMC, which are labeled by injecting fluorescent tracers into the intermediolateral region of the spinal cord at T13-L1 and S1-S2 levels, respectively [388].

8.3 Conclusion

During the past few decades, research in the field of neurourology has led to the emergence of new concepts regarding the neural control of the lower urinary tract and the etiology of lower urinary tract dysfunction. This has stimulated the search for new therapies to treat voiding disorders. In addition to traditional drugs, which target the smooth muscle or postjunctional muscarinic and adrenoceptors, it is now clear that targets at other sites such as afferent neurons, efferent nerve terminals, urothelial cells, and the central nervous system are equally important for drug development. Because micturition is controlled by complex neural circuits distributed throughout the central and peripheral nervous systems that utilize a wide variety of neurotransmitters, it is probable that many different classes of drugs will eventually be used to treat voiding problems. The major challenge is to identify drugs which exhibit "uroselectivity," i.e. affect the lower urinary tract without eliciting undesirable side effects. We hope that this chapter helps understand and update the readers' knowledge for the pharmacology of the lower urinary tract, thereby leading to the future development of new therapeutic modalities of lower urinary tract dysfunction.

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Part IV

Pathology and Pathophysiology

Pathology and Pathophysiology of the Lower Urinary Tract

9

Jean Jacques Wyndaele

9.1 Introduction

The knowledge on the ultrastructure of the lower urinary tract (LUT) has increased substantially during the last decades. This has resulted in the discovery of new structures and a detailed picture of tissue, nerves, receptors, transmitters acting to create sensation, motor relaxation, bladder wall elasticity and muscle contraction. It has led to stronger hypothesis on how bladder and urethra work in normal and in pathological conditions.

To understand why in neurologic conditions different parts of the LUT show specific actions, beside the remaining innervation and changes in these structures, also changes in the microstructure of the tissues involved are important. It is generally agreed that microstructure and function are highly interrelated, and that both influence each other and provoke changes both ways.

Haferkamp summarizes three distinctive patterns occurring separately or in combination: Degeneration associated with impaired detrusor contractility; dysjunction as in detrusor overactivity; myohypertrophy of the detrusor with bladder outflow obstruction [1]. On top of this come the changes related to age, giving alterations also in the neurological impaired LUT. Most patients with neurogenic bladder need alternative ways to regulate filling and special techniques to empty it. These treatments can in their own right lead to extra changes during follow up.

In the following, data from animal studies and from human studies will be discussed. This will show how much is changed in the pathological ultrastructure and what are the consequences for the neurogenic LUT function. Often distinction has been made between changes occurring in lower motor neuron lesions (LMNL) and upper motor neuron lesions (UMNL).

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9.2 Pathology

9.2.1 Bladder Interstitial Cells (BIC)

This "newly" highlighted type of cells in the interstitium of tissues that express the c-kit antigen (Kit(+) cells), have morphologic features that are similar to the described pacemaker cells in the gut, the interstitial cells of Cajal (ICC).

Their role in the LUT will not be identical. There is increasing evidence that these cells play a role in modulating the contractile behaviour of adjacent smooth muscle, and might also be involved in mediating neural control [2]. In the urethra, ICCs have been described as "loose pacemakers" providing multiple, random inputs to modulate urethral smooth muscle activity. The literature suggests that the role of these cells may be more apparent in pathophysiological conditions [3]. It has become clear that BIC just describes number of cells situated between other cells that are generally better-characterised. They are likely to express a variety of phenotypes, which may probably change with UT pathologies, as in neurogenic detrusor overactivity (NDO) [4]. Gevaert et al. [5] studied a possible phenotyping in patients with NDO and found a pronounced shift towards a fibroblastic phenotype.

Reviewing the literature, Kanai et al. [6] state that following spinal cord injury (SCI) intrinsic contractions and spinal micturition reflexes develop, which may stimulate nociceptive and mechanosensitive afferents contributing to NDO and incontinence. The IC mediated activity would start in the lamina propria by responding to urothelial factors. IC may act syncytial through gap junction coupling and module detrusor activity, though the mechanism is unknown as yet.

9.2.2 Structural Changes in the Bladder Wall

The bladder wall in patients with LUT neuropathy shows important histological changes: inflammatory infiltration, oedema and fibrosis of the bladder wall have been frequently

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_9

observed. In the short-term (2–4 weeks) transsynaptic degeneration of cholinergic axon terminals and varicosities happen with widening of the cleft between axon terminal and muscle cells. The degeneration of postganglionic axons is associated with preservation of most adrenergic axons. Restricted regeneration will start quite early: regeneration of cholinergic axons and reformation of cholinergic neuroeffector junctions. Adrenergic hyper innervation is seen as a result from the sprouting of adrenergic axons. Both in cholinergic and adrenergic axons abundancy of large dense core vesicles has been described. Other findings were distorted axonal mitochondria, degenerated myelinated axons, axonal collapse and irregular myelin sheaths, with split sheaths in some, and indications of a persistent or continuing degenerative process [1].

Changes in afferent activity in human after spinal cord injury (SCI) have been extensively presented by de Groat and Yoshimura [7]. In patients with NDO an increased TRPV1, P2X3 and pan-neuronal marker staining in suburothelial nerves has been described. Increased TRPV1 staining has been found in the basal layer of the urothelium. In the cat the VIP-IR C-fibre afferent projections have been shown to expand and to reorganise. Several changes in morphology have been described showing plasticity [7].

In patients with LMNL (n = 4), the detrusor muscle has been studied immunohistochemically, for different neuropeptides. There has been found a decrease in the density of vasoactive intestinal polypeptide-, calcitonin gene-related peptide- and substance P-immunoreactive nerves, but little change in neuropeptide Y- or somatostatin-immunoreactive nerves. The authors conclude that urinary retention, bladder areflexia and deficient sensation may be directly linked to neuropeptide neuropathy in LMNL [8].

Characterizing the specific histological features associated with myelodysplastic bladders, using classical morphometric analysis with the assistance of an automated image analysis system in myelodysplastic stillborn foetuses and patients undergoing autopsy or augmentation cystoplasty, was done by Shapiro et al. [9]. Gross histological analysis showed a marked paucity as well as a significantly diminished size of the muscle bundles. Significantly more interfascicular and pericellular infiltration of the smooth muscle by dense connective tissue was seen, compared to non-myelodysplastic controls. The finding that these changes were seen already in foetuses, enhance our understanding of the relationship of connective tissue proliferation to smooth muscle in the myelodysplastic bladder.

A study aimed at evaluating whether any significant additional histopathological findings can be obtained by taking bladder biopsies from the dome ánd the trigone of the urinary bladder instead of from just one location, in the absence of any visible urothelial lesion in the bladder of patients with neurogenic bladder after SCI (n = 40). In 50%, significant additional findings were obtained by taking samples of both areas. Amongst the pathological findings were e.g. follicular cystitis, squamous metaplasia with or without focal atypia, limited or mild local atypia, extensive glandular metaplasia, intestinal metaplasia, extensive calcification of epithelial denudation, adenomatoid metaplasia, features of interstitial cystitis, mild dysplasia, mild crypt hyperplasia of urothelium. This shows how frequent and in what variety histological changes occur in neurogenic bladder after SCI, and that taking samples from different areas is mandatory to get a reliable investigation [10].

Whether abnormal growth regulation of urothelium may be a predisposing factor for cystitis and vesical neoplasia, was studied in the expression and localization of epidermal growth factor receptor (EGRF) in the vesical urothelium by an immunohistochemical technique, using monoclonal mouse anti-human epidermal growth factor receptor antibody in cold-cup biopsies taken from the trigone of the urinary bladder in SCI patients with neurogenic bladder (n = 18). Abnormal cytoplasmatic localisation was found in the majority. These changes may play a role in the pathogenesis of cystitis, vesical urothelial metaplasia, dysplasia and neoplasia [11].

The presence of nerve fibres in the vesical urothelium and suburothelial from the dome and trigone was demonstrated by routine immunohistochemical technique using commercially available monoclonal and polyvalent antibodies against S-100 and Neurofilament in SCI patients with neurogenic bladder (n = 47). Different grades of hyperplasia were found in the vast majority of cases. The findings made possible to generate hypotheses on the association between C-fibre hyperplasia and response to intravesical pharmacotherapy and the predictive value in identifying those patients who are likely to respond to such therapy [12].

Sphingosine kinase 1 (SPK1) is an enzyme that in humans is encoded by the SPHK1 gene. SSPK1 changes phingosine to sphingosine-1-phosphate (S1P) a lipid messenger with both intracellular and extracellular functions: intracellularly, the regulation of proliferation and survival, and extracellularly, it is a ligand for EDG1. The expression has been studied in patients with neurogenic bladder dysfunction (SCI n = 8; multiple sclerosis n = 2, controls n = 5). Statistically significant increased SPK1 urothelial immunoreactivity was shown but was significantly decreased in the sub-urothelium, muscles and nerves. To determine the role of these findings in the pathophysiology of NDO needs more study [13].

The expression of two types of cation channels, γEpithelial Na(+) Channel (γENaC) and the Acid-Sensing Ion Channel 1 (ASIC1), in the urothelium of controls (n = 4) and in patients affected by NDO (n = 12) was studied. Both markers showed consistent changes either in cell distribution and labelling intensity compared with the controls. A significant correlation between a higher intensity of γENaC expression in the urothelium of patients with NDO and lower values of

bladder compliance was detected. These findings may indicate that changes in γENaC might impair the mechanosensory function of the urothelium, while the increase of ASIC1 might represent an attempt to compensate for the excess in local sensitivity [14].

A histopathologic study in SCI patients (n = 61) with samples taken from the trigone, showed abnormal alterations of bladder tissue in >90%, with especially chronic and subacute types of inflammation. Normal bladder tissue was found only in five cases. Further observation showed fibrosis, oedema and lymphoid hyperplasia. There was no significant correlation between the number of clinical bladder infections per year, the duration of injury, the neurologic level of the spinal cord lesion, and histopathologic types of infections [15].

A similar study, but with biopsies taken from the bladder fundus, also showed abnormal changes in the urothelium in >90%. Again, no significant correlation was found between the number of clinical bladder infections per year, the duration of injury, the neurologic level of the spinal cord lesion, and histopathologic types of infection [16].

A study in children and young adults with myelomeningocele (n = 12) showed abnormal urothelium in 95%. Half had chronic inflammation, three squamous metaplasia. The apical surface of the epithelium in all patients with chronic inflammation had some reactivity with anti-uroplakin antibody. But the cells positive for uroplakin, were scattered along the surface. The apical surface of patients with squamous metaplasia was negative for uroplakin. The findings indicate altered urothelial proliferation [17].

An ultrastructural study of detrusor smooth muscle and intrinsic nerves in patients with NDO (SCI n = 25; brain disorder = 17) and combined upper and lower neuron deficit (meningomyelocele n = 9) was done by Elbadawi et al. All displayed the complete dysjunction pattern of detrusor overactivity. Most had degeneration and regeneration of intrinsic axons but limited muscle cell degeneration, irrespective of detrusor contractility. The brain disorder group had many more ultrastructural normal axons than the meningomyelocele and SCI group. A conclusion from this study could be that morphologic markers not only may distinguish neuropathic from non-neuropathic bladder dysfunction, but also may point to the anatomical level of the neurogenic deficit [18].

Results of biopsy studies in 46 patients with NDO (meningomyelocele n = 9, SCI n = 25, brain disorder n = 12) show intermediate junctions of muscle cells to be absent or reduced, while dominant intimate cell apposition with much narrower junction gaps were seen.

A study by the same group was done in a larger number of patients with NDO (meningomyelocele n = 9, SCI n = 25, brain disorder n = 25). Intermediate junctions of muscle cells were absent or reduced in a majority, which instead had dominant intimate cell appositions with much narrower junctional gaps. Muscle cell degeneration was observed in 74% (of those where the test was done) with normal contractility and in 74% of those with impaired detrusor contractility. No particular changes were associated with functional bladder outlet obstruction due to detrusor-sphincter dyssynergia (DSD). One clinical conclusion made is that the lack of relationship between muscle cell degeneration and detrusor contractility probably reflects limitations of urodynamic measurement of contractility in patients with SCI and meningomyelocele [19].

Evaluation of changes in intrinsic detrusor nerves is a third study by the same group (meningomyelocele n = 9, SCI n = 25, brain disorder n = 12). Axonal degeneration was observed most with discernible intrinsic nerves. Structurally normal axons were much more common in brain disorder than in meningomyelocele or SCI. Axonal regeneration was observed in most biopsies (76%) and was independent of the duration of neurogenic bladder dysfunction. Axon sprouts were observed in 38%, and copeptidergic axons formed 20% in contrast to less than 1% in normal detrusor. Activated Schwann cells were observed in all but 1 biopsy. The axonal changes were not associated with the level or degree of spinal cord lesion. As combined degeneration and regeneration is the characteristic change in intrinsic nerves of detrusor in UMNL, they offer the possibility of clinically recognizing neuropathic contribution to a dysfunctional detrusor, as well as the potential to distinguish its spinal versus supraspinal etiology [20].

A specific study on C fibres has been done in patients with NDO and a control group (tropical spastic paraparesis n = 8; multiple sclerosis n = 23 and SC disease n = 12). The mean nerve profile diameter was greater in patients with tropical spastic paraparesis compared to controls and patients with multiple sclerosis. Some sparse urothelial innervation by naked axonal varicosities were seen but were more frequent in the superficial layer of the lamina propria. In deeper layers close membrane contacts between axonal varicosities and cells with cytological characteristics of myofibroblasts were described. If these findings offer a possibility to assess the effect of intravesical treatments on these nerves needs to be determined [21].

In two groups of patients with denervation of the bladder after excision of the rectum, bladder biopsies were examined after 7 weeks or 10 months after operation respectively. A control group was included. In control patients, the ratio of cholinesterase positive nerves to the number of smooth muscle nuclei was significantly greater than in patients with denervation of the bladder studied soon after operation. Degenerate nerve terminals were observed on electron microscopy in these patients. No increase in the density of adrenergic nerves was observed in either group of patients with denervation of the bladder. In the long term, a greater density of cholinergic innervation was noted compared with

patients studied soon after operation. In addition, nerve terminals, similar in appearance to those of control patients, were observed on electron microscopy. These findings are consistent with partial regeneration of autonomic nerves. Histological examination of bladder biopsies may be less sensitive in the long term [22].

9.2.3 Transmittors and Receptors

Purinergic mechanosensory transduction occurs where ATP, released from urothelial cells during distension of bladder and ureter, acts on P2X3 and P2X2/3 receptors located on suburothelial sensory nerves to initiate the voiding reflex, via low threshold fibres, and nociception, via high threshold fibres. While in normal conditions the purinergic component of parasympathetic (PS) co-transmission is very limited, in the neuropathic bladder the purinergic component is increased to 40% [23].

An examination of the immunohistochemical expression of muscarinic receptors types 1, 2 and 3 in the bladder urothelium and sub-urothelium of patients with NDO, showed decreased suburothelial muscarinic receptor 1 and 3 immunoreactivity. After successful botulinum neurotoxin treatment urothelial muscarinic receptor 1 and 3 immunoreactivity was increased (restored) but not in type 2. Receptor levels had inverse correlations with urgency and frequency [24].

Apostolidis et al. investigated endothelial nitric oxide synthase (eNOS) immunoreactivity, and the vascular markers von Willebrand Factor (vWF) and vascular endothelial growth factor (VEGF) in bladder biopsies from patients with NDO before and after treatment with intravesical resiniferatoxin (n = 19, control group n = 8). They found eNOS immunoreactivity in the sub-urothelium and less often in the urothelium, with a distribution indicating a location in small blood vessels at the urothelium-suburothelium junction. vWF showed a similar location. There was a trend to higher eNOS values before treatment in those responding than in those not responding to resiniferatoxin, and a significant reduction in eNOS immunoreactivity after successful treatment, possibly suggesting that increased vasculature or vasodilatation in the suburothelium may be necessary for successful intravesical treatment. There was a significant increase of VEGF pre-treatment in responders [25].

9.2.4 Bladder Wall Fibrosis

In an animal model of multiple sclerosis (MS), morphometric and molecular alterations of the bladder were evaluated. Significant increase in the bladder weight-to-body weight ratio was observed with increasing neurological impairment. Morphometric analysis showed marked bladder remodelling with increased luminal area and tissue hypertrophy. The ratio of connective tissue to muscle increased significantly. Marked increases in mRNA expression of collagen type I α(2), tropoelastin, transforming growth factor-β3, and connective tissue growth factor (CTGF) were observed, as well as a decrease of mRNAs for smooth muscle myosin heavy chain, nerve growth factors, and muscarinic and purinergic receptors. These results suggest that bladder remodelling may be due to enhanced expression of CTGF and increased growth of connective tissue [26].

With morphometric and histochemical techniques the relative volume of connective tissue in the bladder wall has been evaluated and the two major types (I and III) of collagen within the bladder wall measured, in 29 patients with dysfunctional bladders necessitating bladder augmentation, not only of neurologic origin. The low bladder compliance proved secondary to an alteration in the connective tissue content of the bladder wall [27].

Compérat et al. evaluated if injections with botulinum toxin (BTX) had an influence on bladder wall fibrosis. In 45 patients with NDO significantly less fibrosis was seen when being treated with BTX. Moreover a trend was observed that responders had less fibrosis and oedema of the wall than non-responders [28].

Mast cells have been associated with a fibrogenic response in inflammatory conditions. Myelodysplastic bladders are characterized by increased mast cells in the detrusor muscle layer compared to control bladders, as well as mast cell degranulation and increased connective tissue deposition. Types I and III collagen mRNA localized to fibroblasts surrounding detrusor muscle fascicles have been demonstrated, while only collagen III mRNA localized to cells within connective tissue infiltrate the muscle bundles in myelomeningocele bladder tissue. These findings indicate that bladder fibrosis may be mediated by mast cell chymase stimulation of collagen synthesis [29]. In an immunohistochemical study in non-compliant bladders in patients with SCI and with myelodysplasia, regulation of collagen synthesis in bladder fibrosis was characterized by both transcriptional and post-transcriptional mechanisms, depending upon the etiology of the fibrosis [30].

9.2.5 Sphincter

The adrenergic and cholinergic innervation of the smooth and striated muscle components of the urethra from SCI patients with detrusor sphincter dyssynergia have been investigated neurochemically and histochemically by Lincoln et al. Catecholamine fluorescence histochemistry provided no evidence for the presence of adrenergic nerves associated with the skeletal muscle. Choline acetyltransferase activity in the skeletal muscle and the noradrenaline content of the smooth muscle in mid and distal urethra, were significantly

lower in cervical lesions than in thoracic lesions. In the proximal urethra noradrenaline levels were similar in both SCI level groups. These data suggest that no adrenergic nerves are associated with striated muscle fibres in the intrinsic external urethral sphincter in UMNL [31].

The same group investigated catecholamines in the intrinsic external urethral sphincter from patients with LMNL and detrusor areflexia. Varicose adrenergic nerves were demonstrated in the smooth muscle. Adrenergic nerve fibres also were found along the edge of individual striated muscle fibres as well as around striated muscle bundles. Blood vessels in both regions of the urethral sphincter were innervated by adrenergic nerves, indicating a substantial presence of adrenergic nerve fibres in relation to smooth and striated muscle in the urethra. The function of these nerve fibres is not certain as yet [32].

A third study from this group investigated in three patients (1 SCI at C1–2, 2 SCI at T10) histochemically and immunohistochemically, the adrenergic and vasoactive intestinal polypeptide (VIP)-immunoreactive nerves. Dense VIP-immunoreactive but not adrenergic nerves were found in the urethral smooth muscle, around the blood vessels and at the base of the mucosa in the patients with thoracic lesions. In contrast, adrenergic but VIP-immunoreactive nerves were found associated with the smooth muscle of the urethra and around the blood vessels in the patient with a cervical lesion. No adrenergic nor VIP-immunoreactive nerves were found around striated muscle fibres of the intrinsic external urethral sphincter [33]. Also was found the NPY-and VIP-containing-fibres in striated muscle of the intrinsic external urethral sphincter were increased in patients with a-reflexic bladder compared with those with DSD after SCI [34].

9.2.6 Influence of Indwelling Catheter

In order to evaluate if chronic urinary catheters induce histological changes in the bladder with time, several studies have been done.

The exact aetiology of such changes is postulated to arise from inflammation and local tissue response. Delnay et al. studied the incidence of non-malignant histological change in bladder biopsies of patients with chronic indwelling urinary catheters in 208 SCI patients with indwelling transurethral or suprapubic catheter for >8.5 years. Biopsies were obtained from 4 to 6 different sites. A total of 17 patients were identified with malignancy (10 with squamous cell carcinoma, 5 transitional cell carcinoma, 2 with adenocarcinoma). Premalignant changes occurred in 23% (keratinizing squamous metaplasia or cystitis glandularis). A spectrum of inflammatory and proliferative pathological conditions were identified. The findings underscore the need to have an active surveillance in such patients [35].

Vaidyanathan et al. hypothesise that the following histological lesions are seen more frequently in the neuropathic bladder of SCI patients with long-term indwelling catheters: papillary or polypoid cystitis; widespread cystitis glandularis; moderate to severe, acute and chronic inflammatory changes in bladder mucosa; follicular cystitis; squamous metaplasia; and urothelial dysplasia [36]. Wall et al. demonstrated in SCI patients with a chronic indwelling bladder catheter (n = 37) that inducible NOS was expressed in inflammatory macrophages in areas of chronic inflammation in the urothelium. This expression may potentially lead to the sustained production of NO and its oxidative products, the nitrosation of urinary amines and the formation of potentially carcinogenic nitrosamines in the bladder [37]. Vaidyanathan et al. evaluated the expression of cytokeratin 20, in SCI patients (n = 63). Squamous metaplasia and absent immunostaining for cytokeratin 20 was found in 8 biopsies. In the remaining 53 cases with an intact umbrella cell layer of the urothelium, immunostaining for cytokeratin 20 was seen only in 10 biopsies. The authors hypothesize that there may be an underlying metaplasia or that changes in the neuropathic bladder affect urothelial differentiation. Other factors, such as impairment of voluntary voiding in SCI patients, could affect expression of markers such as cytokeratin 20 [38]. Immunostaining for cytokeratin 14 was used in SCI patients to identify an early phenotypic switch from transitional to squamous epithelium in the urothelium, which is mostly not yet evident on examination of routine H&E staining. This early identification might be used to decide that a change of bladder management needs to be considered in order to prevent recurrent urinary infection and progression of squamous metaplasia [39].

9.2.7 Prediction of Upper Tract Deterioration

In 39 patients with long existing NDO, full-thickness bladder biopsies were examined. The severity of detrusor fibrosis was a significant risk factor for UUT deterioration [40].

9.2.8 Changes in Intestinal Epithelium Used for Derivation

Segments of bowel are used for reconstruction/derivation in various pathological conditions such as poorly compliant neuropathic bladders. The effect of the contact between the bowel epithelium and urine has been studied by different authors.

In an ileal neobladder (n = 15) no significant changes were observed 3 months after surgery. After 6 and 12 months, the structure of the microvilli was modified significantly. No other substantial changes were observed after 24 months

[41]. At mean 14 months after augmentation cystoplasty, varying degrees of villous atrophy, increased numbers of Paneth and goblet cells were found, with severity unrelated to the time since surgery. These may be adaptations of the bowel tissue to counteract noxious effects of urine and to maintain an epithelial function in the bladder [42].

Biopsy specimens from continent caecal reservoir for urine and from its ileal nipple valve were studied after 2–9 years in 10 patients. In the colonic epithelium, shortening of microvilli, in some cases with random orientation and numerical reduction-changes were seen, unrelated to the time since reservoir construction. Filamentous core rootlets were also randomly oriented and numerically diminished. Glyco-calyceal bodies were present in most cases. Mucosal oedema and reduced numbers of goblet cells were found in 6 and increased amount of collagen in 2. In the ileal nipple valve mucosa, there were no microvillous changes, but metaplastic formation of glyco-calyceal bodies was interpreted as adaptation to physiologic conditions comparable with those in the reservoir's colonic mucosa. Collagen increase was found in 2 of the nipple valves. Neurogenic processes, enterochromaffin cells and Paneth cells were always well preserved in normal amounts in the caecal as well as the ileal mucosa [43].

9.3 Pathophysiology

When a neurologic pathology affects the innervation of the LUT, the dysfunctions that will result depend on the site of the lesion, its extent, the evolution of the neurologic cause and the changes induced by the deficit during follow up.

For a long time neuro-urological pathology has been divided into UMNL (which include suprapontine = cerebral and suprasacral = brainstem, and spinal cord pathology), and LMNL (comprising sacral and subsacral = cauda equina and peripheral nerve). Lesions at the level of the brainstem lead mostly to short-term survival. They are only infrequently encountered in neuro-urological practice.

Madersbacher et al. have presented a schematic overview of combinations of bladder and sphincter dysfunction that can be found in LUT neuropathy [44]. Very recently Powell proposed a new step in classification of the neurogenic bladder: SALE (Stratify by Anatomic Location and Etiology). This classification is grounded on seven categories, each having a neurologic defect in a distinct anatomic location. In addition, the presence or absence of bowel dysfunction and autonomic dysreflexia is reported.

In the future, as more definite prognostic information can probably be obtained from biomarkers. Urinary nerve growth factor (NGF) and urinary brain-derived neurotrophic factor (BDNF) levels can then be added to the classification. The SALE system should efficiently describe a patient suffering from neurogenic bladder and simultaneously inform the most appropriate treatment, follow-up regimen, and long-term prognosis.

9.3.1 Suprapontine Lesions

Patients with pathology above the pons, as with stroke, head injury, et al., have no direct lesion of the pontine micturition center (PMC) and often continue to have reflex contractions of the detrusor. However, they may lose cerebral input to LUT and bowel function. They mostly continue to have a normal synergic LUT function, as the coordination out of the pons between bladder and sphincter continues to function.

However, such patients may purposely increase sphincter activity during NDO [45] to prevent incontinence (UUI). Such *pseudo-dyssynergia* is not easy to distinguish from true DSD on a urodynamic trace. Urinary incontinence in suprapontine lesions is due to NDO, or to lack of inhibition of the micturition reflex [46].

In suprapontine lesions a neurologic LUT dysfunction may be a direct consequence of the neurologic lesion, but may also be due to or changed by motor and cognitive dysfunctions, which may cause functional incontinence. It is easy to understand how important loss of mobility and of initiative/cognition can be.

Modern functional neuroimaging has given much extra knowledge about how cerebral suprapontine regions are related to the LUT function. The location and extent of a suprapontine lesion will determine the resulting symptoms and if they are reversible or not [47]. A recent literature review accepts clear roles of the supplementary motor area, dorsal anterior cingulate cortex, lateral prefrontal cortex, thalamus, insula [48]. The cerebral control of the urethral sphincter also depends on voluntary and involuntary control by different regions of the brain [49].

Suprapontine lesions give a loss of inhibition of the pontine micturition centre with resulting storage dysfunction. Spontaneous involuntary DO can be seen, different from NDO after supra-sacral SCI.

Normal uroflowmetry and normal post voiding residual (PVR) may be expected, if no age related outflow obstruction is present. Detrusor underactivity (DU) has been reported, as well as DO with impaired contraction (DOIC) [50]. There may be loss of one or more of the cerebral activities, such as volitional timing of emptying, inhibition of bladder, LUT sensations and integration with other systems and activities of daily life (ADL).

New knowledge is developing. The CNS, once considered to be an immune-privileged area may instead be an active surveillance site, with bi-directional communication with the immune system. This finding has led to a significant interest in neuroimmunological interactions and investigation into the

role of the immune system in the pathology of various neurological disorders. The proposal has been made that the relationship between peripheral immune cells, the brain, and the urologic system should be considered as an additional possible mechanism in urologic diseases, and that immunotherapy might be an alternative therapeutic strategy in treating neurogenic bladder dysfunction [51].

9.3.2 Pontine Lesions

These are rarely compatible with life. But if survival is possible, and the dorsal pontine tegmentum, the seat of the PMC remains functioning. NDO, and DSD may be seen, as e.g. in multiple system atrophy (MSA; formerly known as Shy-Drager syndrome).

9.3.3 Suprasacral Spinal Cord Lesions

When a lesion is located in the spinal cord below the pons/medulla oblongata and above the sacral level, DSD is a common finding. Incontinence may still be caused by NDO, but clinically total or partial retention due to the DSD may be seen.

A SCL above the lumbosacral level eliminates, depending on extent of the lesion, voluntary and supraspinal control of micturition, leading to spinal NDO mediated by spinal reflex pathways [52]. One should realise that the reflex bladder function is very different from normal: different afferent fibres = C-fibres-possibly mediated by NGF [53]; poorly sustained detrusor contractions; DSD; previously inactive stimuli can elicit or influence the LUT activity, such as by tapping on lower abdomen, body movement et al. Sensation in the LUT may be partly or completely saved [54]. It is important to realise that the urodynamic outcome is specific for every single patient, which makes proper evaluation mandatory [55].

DSD creates a functional outflow obstruction and results in impaired voiding, high residual urine, too high intravesical pressure development and can lead to structural damage as severe trabeculation, vesicoureteral reflux, hydronephrosis and renal impairment. Different types of DSD have been described such as only at start of NDO, at the end, periodically during NDO or changing after some time into a relaxation which permits outflow of urine [56].

A lesion resulting in a completely transsected lower part of the spinal cord may also hurt the conus and lead to LMNL effects.

Autonomic dysreflexia is a clinical event which can be potentially life threatening. It occurs mainly when a SCL above T6 creates outflow of afferent potentials from the bladder, bowel or other stimuli towards the very extensive intestinal vascularisation. This creates vasoconstriction and significant hypertension. The body's response is a reflex bradycardia and vasodilatation which can only occur in areas still under suprapontine control i.e. above the lesion. This results in vasodilation, headache, red skin of face and superior thorax and can lead to cerebral oedema and death. As attacks of DSD are often provoked by urological investigations and treatment, all involved should be well aware of the risk and be prepared to prevent and treat properly and urgently [57].

9.3.4 Incomplete Suprasacral Lesions

Mainly four types of incomplete suprasacral SCLesions are known:

- Anterior cord syndrome, due to disruption of the anterior spinal artery leading to reduced or absent motor activity and pain/temperature sensation while proprioception is retained,
- Posterior cord syndrome e.g. from tabes dorsalis which affects only proprioception
- Lateral cord syndrome (Brown Sequard) with ipsilateral loss of power and proprioception and contralateral loss of pain and temperature sensation
- Central cord syndrome, due to traumatic neck hyperextension during a fall [58].

Incomplete suprasacral lesions lead to variable LUT dysfunction:

- Anterior cord injury gives in the majority NDO. DSD is possible depending on exact location and extent of the lesion, especially when the lateral columns are affected [59]. Bladder sensation may be spared, if the dorsal columns are intact [60].
- Brown Sequard syndrome may again give very different dysfunctions: NDO, detrusor areflexia, DSD [61].
- Central cord syndrome may give different types of dysfunction as detrusor areflexia, DSD, NDO, detrusor underactivity [62]. Sensation will mostly be preserved [63].

9.3.5 Sacral and Subsacral/Cauda Equina Lesions/Peripheral Neuropathy

Lesions of the conus medullaris and cauda have high probability that the nuclei in the conus will be destroyed, creating decentralization and an areflexic detrusor [64]. Clinical differentiation between sacral and subsacral is difficult [65].

When lesion has occurred to Onuf's nucleus, with a mixed autonomic/somatic function, paralysis of the sphincter and pelvic floor muscles may result. Sensory deficit can be

present though the sensory afferent pathway through the hypogastric nerves is mostly saved giving possibility to feel pain and slight sensation of bladder filling. If there is extensive autonomic damage, the bladder neck remains open.

Peripheral neuropathies (as in diabetes, alcohol abuse, Guillain Barré et al.) [27, 28], can cause impairment of both parasympathetic and somatic motor function: the detrusor can be underactive or areflexic and the external sphincter can be paralyzed.

9.4 Conclusion

There are new findings in animal and human research showing more clearly the complexity of the extensive innervation of the LUT, from bladder wall to cortex, and the dysfunctions that follow a neurologic disease or trauma. The pathophysiology in many conditions has been studied and a lot of clinical information has become available.

These data clearly show that a very specific type of dysfunction will be found in every single patient. Therefore a more elaborate investigation is needed in most, unless no treatment will whatever follow from such diagnostic data. More research will become available in the near future which will help further to better understand and treat the neurogenic bladder in all its aspects.

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Part V

Epidemiology

Epidemiology of Neurogenic Lower Urinary Tract Dysfunction

10

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10.1 Introduction

Neuro-urological symptoms/dysfunction result from a wide range of neurological disorders [1, 2]. The site of the lesion in the neurological axis determines the general pattern of lower urinary tract dysfunction, which is reflected in the patient's symptoms (Fig. 10.1) [1]. Data on the prevalence/incidence of the underlying neurological disorder and the consecutive neuro-urological symptoms/dysfunction vary widely reflecting the high variability in the neurological cohort (i.e. early, medium and late stage of disease, limited number of included patients, often low level of evidence studies). The epidemiology of the neuro-urological data is summarized in Table 10.1.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_10

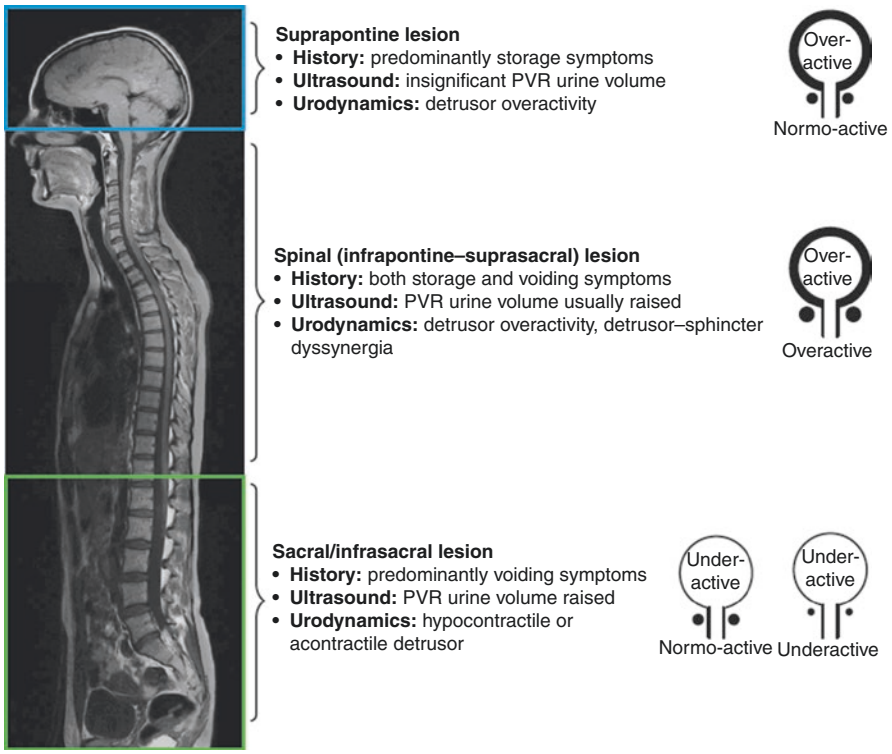

Fig. 10.1 Patterns of lower urinary tract dysfunction following neurological disorder. The pattern of lower urinary tract dysfunction following neurological disorder is determined by the site and nature of the lesion. The blue box denotes the region above the pons and that in green denotes the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. *PVR* post void residual. Figure from Panicker et al. [1] with permission from Elsevier

Table 10.1 Epidemiology of neuro-urological disorders and consecutive neuro-urological symptoms/dysfunction

Suprapontine and pontine lesions		
Neurological disorder	Frequency in general population	Neuro-urological symptoms/dysfunction
Brain tumours	29.2/100,000/year in adults (20+ years), (8.7 malignant [most common malignant tumor: glioblastoma about 47%], 20.4 benign [most common benign tumor: meningioma 53%]) [3]	Urinary incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [4]
Dementias [5] • Alzheimer's disease (60–80%) • Vascular disease (10–20%) • Other diseases (10%) [Lewy bodies, Parkinson's disease, normal pressure hydrocephalus, fronto-temporal degeneration, Creutzfeld-Jakob disease, multiple causes]	17.2/1000/year [6]	Overactive bladder, urinary urgency incontinence, detrusor overactivity 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, normal pressure hydrocephalus, Binswanger, Nasu-Hakola, Pick disease [7] Urinary incontinence 3 times more frequent in geriatric patients with dementia than without [8]
Cerebral palsy	3.1–3.6/1000 in children aged 8 years [9]	LUTS 36–76%, storage symptoms more common than voiding symptoms, urinary incontinence most frequent symptom 20–94%, detrusor overactivity 9–97% [10]
Normal pressure hydrocephalus	2–20/100,000/year [11]	Nocturia, urinary urgency incontinence, 100% detrusor overactivity [12], LUTS improve following ventriculo-peritoneal shunting [13]
Parkinsonism • Primary Parkinsonism: Idiopathic Parkinson's disease (IPD): 75–80% • Secondary (acquired) Parkinsonism (2%) • Atypical Parkinsonism (Parkinson's-plus) (18%): – Progressive supranuclear palsy – Multiple system atrophy (MSA) [Shy-Drager syndrome: MSA with postural hypotension] (MSA-P: Parkinsonism predominent, MSA-C: cerebellar predominant) – Corticobasal degeneration – Parkinsonism-dementia complex	IPD (age-standarized) incidence 14/100,000/year, ≥65 years old: 160/100,000/year [14] IPD second most prevalent neurodegenerative disorder after Alzheimer's disease, rising prevalence with age MSA incidence ≥50 years old: 3/100,000/year [15]	LUTS frequency 30% at onset, 70% after 5 years. Storage symptoms: Nocturia (78%), overactive bladder, urinary urgency incontinence, detrusor overactivity (36–93%) [15] MSA: Overactive bladder and detrusor overactivity at the initial phase, intrinsic sphincter deficiency and impaired contractility appear as the disease progress. Complications of neuro-urological symptoms (infections) account for a major cause of mortality in MSA [16] Impaired detrusor contractility seems to be the urodynamic finding distinguishing MSA from IPD [17, 18]

Table 10.1 (continued)

Suprapontine and pontine lesions		
Huntington's disease	Prevalence 0.4–7.3/100,000 [19]	Overactive bladder (women/men: 40%/54%), urinary urgency incontinence (women/men: 43%/29%), voiding symptoms (women/men: 40%/25%), detrusor overactivity (17%), detrusor sphincter dyssynergia (42%) [20]
Cerebrovascular accident (stroke)	450 cases/100,000/year (Europe) [21], 10% of cardiovascular mortality	Nocturia, overactive bladder, urinary urgency incontinence, detrusor overactivity, other patterns less frequent [22] 57–83% of neuro-urological symptoms at 1 month after stroke, 71–80% spontaneous recovery at 6 months [23] Persistence of urinary incontinence (UI) correlates with poor prognosis [24]
Traumatic brain injury	235/100,000/year [25]	44% storage dysfunction, 38% voiding dysfunction, 60% urodynamic abnormalities [26]
Lesions between caudal brainstem and sacral spinal cord		
Spinal cord injury (SCI)	Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million [27]	NDO and DSD (up to 95%) and detrusor underactivity (up to 83%) depending on the level of the lesion [28]
Spina bifida (SB)	Spina bifida 3–4/10,000. Lumbar and lumbosacral form are the most common (60%) [29]	Bladder function is impaired in up to 96% of SB patients [30]
Other causes – Spine and spinal cord tumors – Infections/para-infectious (transverse myelitis) – Cervical/thoracic disk disease – Lesion following spinal anesthesia/spine surgery	Rare	Storage and voiding symptoms, depending on lesion level
Disseminated central disorders		
Multiple sclerosis (MS)	Incidence: 9.6/100,000/year (11.5 in women and 4.8 in men) [31]	Ten percent of MS patients present with LUTS at disease onset, 75% of patients will develop it after 10 years of MS [32] Detrusor overactivity 86%, detrusor sphincter dyssynergia 35%, detrusor underactivity 25% [32]
Lesions of the peripheral nervous system		
Lumbar/sacral spine – Disk disease – Spinal stenosis – Tumors	Lumbar disc disease prevalence 1–3% (about 95% L4-L5 or L5-S1), male/female ratio 2:1 [33] Lumbar spinal stenosis prevalence 5.7% [34]	LUTS prevalence in lumbar disc disease 27–68%, most commonly voiding dysfunction due to acontractile/hypocontractile detrusor [35]
Iatrogenic pelvic nerve lesions	Radical pelvic surgery for colorectal cancer, gynecological cancer, prostate cancer (multimodal therapy: surgery, radiotherapy, chemotherapy) Non-radical gynecological surgery (incontinence/prolapse/endometriosis surgery), colorectal surgery, vascular surgery	Voiding symptoms >> storage symptoms After total mesorectal excision (TME): 10–30% voiding dysfunction [36]
Peripheral neuropathy • Diabetes mellitus • Other causes – Alcohol abuse – Lumbosacral herpes zoster, genital herpes – Human Deficiency Virus (HIV) – Guillain Barré syndrome – Porphyria – Sarcoidosis – Sacral agenesis	Global prevalence (age-standardized) of diabetes mellitus 8.5% [37] Incidence of Guillain-Barré syndrome 1–2/100,000/year [38]	Overactive bladder, urinary urgency, incontinence, detrusor overactivity, hyposensitivity and detrusor underactivity (often at later phase) [39]

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Part VI

Classification

Classification and Terminology of Neurogenic Lower Urinary Tract Dysfunction

11

Helmut Madersbacher and Jerzy B. Gajewski

11.1 Classifications According to the Involvement of the Nervous System

Decades ago two types of bladders were differentiated: one with a preserved sacral micturition reflex and the other without it. Thus the terminology of "reflex bladder vs. autonomous bladder" developed. Another type of bladder was described as "uninhibited", when it resulted from an incomplete spinal cord injury presumably causing a reduction of central inhibition manifested by urgency and urge incontinence. Following this concept of importance of the sacral segments for reflex micturitions the lesions were differentiated into supranuclear (= suprasacral), nuclear (= sacral) and infranuclear (=subsacral) [1]. These terms indicate a distinct neuro-urological pathology, allowing to differentiate between Upper Motor Neuron Lesion (UMNL), including suprasacral spinal cord-, brain stem- and cerebral lesions, and Lower Motor Neuron Lesion (LMNL), comprising sacral (conus medullaris), subsacral (cauda equina) and peripheral nerve lesions and mixed lesions. This is a considerable simplification and anatomically inaccurate, so the categorization into lower versus upper motor neuron lesions should no longer be supported. The ICI (2017) classifies complete suprasacral lesions as "distal autonomous cord" and the complete sacral/subsacral lesions as "no distal autonomous cord" [2]. If the disorder or injury has its origin purely in the nervous system the disruption can be regarded as primarily neurogenic, however as soon as the lower urinary tract becomes involved it then contains both a neurogenic as well as a LUT (structure) component. Beside the level of lesion in a reference to the sacral cord segments its extent, for instance complete versus incomplete, and also the duration has to be determined. The latter is important as recurrent urinary tract infections and/or recurrent bladder overdistension may change structure and function of the lower and upper urinary tract. E. Bors and A. E. Commar, in their book "Neurological Urology" (1971) accomplished a classification incorporating also the completeness or incompleteness of the lesion, and whether the dysfunction is balanced or imbalanced [3]. This classification is based upon neuronal involvement by its extent and its effect on micturition (see Fig. 11.1). However before some neurological lesion mature and can be defined, there is a period of **Spinal Shock** which is usually temporary, following acute neurologic insult or SCI and is characterized by loss of sensory, motor and reflex activity below the level of injury. **NLUTD in Spinal Shock** is usually a temporary complete painless urinary retention.

In Chapter 2 of this book Jean-Jacques Wyndaele, in the subchapter on "Physiology", classifies neurogenic LUT disorders in those due to suprapontine lesions, to pontine lesions, to suprasacral spinal cord lesions and due to lesions of the conus, the cauda equina and peripheral nerves, moreover he mentions that mainly four types of incomplete suprasacral SCI lesions are known:

1. The anterior cord syndrome, caused by a disruption of the anterior spinal archery resulting in a reduced or missing motor and pain/temperature sensation, but proprioception (posterior horns!) are retained;
2. The posterior cord syndrome, which may affects only proprioception;
3. The lateral cord syndrome (Brown Sequard) with ipsilateral loss of power and proprioception and contralateral loss of pain and temperature sensation; and
4. The central spinal cord syndrome (Schneiders syndrome) due to traumatic neck hyperextension during a fall.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_11

Fig. 11.1 Historical classification from Bors and Commar 1971

Neuron lesion	Synonyms
A. Sensory neuron lesion	Sensory paralytic bladder,
(1) Incomplete, balanced;	Atonic bladder
(2) Complete, imbalanced	sensory type bladder,
B. Motor neuron lesion	Motor paralytic bladder,
(1) Balanced;	motor type bladder
(2) Imbalanced	
C. Sensory- motor neuron lesion	
I (1) UMNL, complete, balanced	Normal cord bladder, reflex bladder, automatic bladder, efficient automatic reflex bladder, spinal reflex bladder, uncontrolled reflex micturition, involuntary reflex bladder
I (2) UMNL, complete, imbalanced	Atonic-autonomous-hypertonic bladder, inactive, shocked bladder, hypotonic bladder automatic reflex bladder, inefficient automatic reflex bladder,
I (3) UMNL, incomplete, balanced	Uninhibited neurogenic bladder, uninhibited bladder, voluntary neurogenic bladder, voluntary reflex bladder
I (4) UMNL, incomplete, imbalanced	
UMNL=Upper Motor Neuron Lesion	
II (1) LMNL, complete, balanced	Autonomous bladder, automatic bladder, automatic bladder, passive micturition automatische Blase
II (2) LMNL, complete, imbalanced	
II (3) LMNL, incomplete, balanced	
I (4) LMNL, incomplete, imbalanced	
I Mixed Lesions	
(1) Upper somatomotor neuron, Lower visceromotor neuron	
(2) Lower somatomotor neuron, Upper visceromotor neuron	
(3) Normal somatomotor neuron, Lower visceromotor neuron	
LMNL=Lower Motor Neuron Lesion	

11.1.1 Suprapontine Lesions (SPL)

Why should a classification distinguish between suprapontine and pontine cerebral lesions? Suprapontine and pontine lesions are characterised by reduced or missing inhibition of the pontine micturition centre from higher cerebral centres during storage dysfunction, urodynamically phasic or terminal DO may be observed. One has to be aware that DO due to cerebral diseases is different from DO with suprasacral spinal cord lesions in many regards including risks for upper urinary tract damage, aims of therapy and therapeutic strategies.

With **suprapontine lesions (SPL)** the coordination (synergia) between detrusor and sphincter is preserved and their characteristics can be summarised as following: voiding is correct, but location and timing of the micturition is wrong. These facts may be a direct consequence of the neurogenic

lesion, but may also be due to cognitive motor deficits (as in dementia) causing "functional" incontinence. Therefore SPL is a neurological lesion above the pons (forebrain or midbrain). **NLUTD** include a reflex contraction of the detrusor with impaired cerebral regulation and central inhibition and usually synergistic voiding/bladder emptying. Lesions resulting from cerebral or brainstem lesion with preservation of the pontine micturition centre (PMC) are cerebrovascular disease, degenerative disease, hydrocephalus, intracranial neoplasms, traumatic brain injury (the list is incomplete). This may lead to inability to initiate voiding, inappropriate timing of bladder emptying, detrusor overactivity (DO) and DO incontinence.

Pontine lesions (PL) are rare as they are rarely compatible with life. However, if patients survive, DO or detrusor underactivity may be seen according to the localisation and extent of the lesion as well as detrusor-sphincter-dyssynergia (DSD), because detrusor and sphincter are coordinated in the brain stem, presumably via the M- and the L-regions.

11.1.2 Suprasacral Spinal Cord Lesions (SSL)

With a lesion located in the spinal cord below the pons/medulla oblongata and above the sacral cord spinal neurogenic DO combined with DSD is a common finding resulting clinically in uncontrollable overactive detrusor contractions with or without incontinence ("spinal reflex micturition"). This reflex is affected on the afferent side by C-fibres, most probably by NGF. The detrusor contractions may appear early during the storage phase, are often poorly sustained and together with DSD result in incomplete voiding. DSD creates a functional outflow obstruction with important consequences to the lower and upper urinary tract. Therefore SSL is a neurological lesion in suprasacral spinal cord and/or pons. **NLUTD** include DO and DO incontinence are common, with or without detrusor sphincter-dyssynergia (DSD), often resulting in a significant post void residual (PVR) and "high pressure" bladder.

If the lesion persists after resolution of the spinal shock bladder sensation may be somewhat preserved (incomplete lesions) but voluntary control of the micturition reflex arc is lost. Altered function of the sympathetic spinal centre in the thoraco-lumbar spinal cord may alter blood pressure control. Complete SSL above T6 may be associated with autonomic dysreflexia (see also Chapter 2 by JJ Wyndaele) when there is residual sympathetic nucleus function; this should be included in the description of the lesion.

Autonomic Dysreflexia is a syndrome resulting from upper thoracic (above T6) or cervical spinal cord injury, elicited by a stimulus in the field of distribution of the autonomous sympathetic nucleus, characterised by unregulated sympathetic function below the lesion and compensatory autonomic responses. It is potentially a medical emergency characterized by hypertension, bradycardia, severe headaches and flushing above, with pallor below the cord lesion, and sometimes convulsions.

11.1.3 Sacral Spinal Cord Lesion (SSCL)

Sacral Spinal Cord Lesion (SSCL) is a neurological lesion in the sacral spinal cord. **NLUTD** findings include acontractile detrusor with or without decreased bladder compliance and usually with impaired sphincter activity. There is a loss of parasympathetic control of the detrusor and a somatic denervation of the external urethral sphincter. Sensory impairment is typically associated with a complete lesion. Some afferent pathways may remain intact due to potential preservation of hypogastric afferents. Some patients may have stress urinary incontinence (SUI) due to sphincter deficiency (loss of Onuf's nucleus).

11.1.4 Infrasacral (Cauda Equina and Peripheral Nerves) Lesion (CEPNL)

Infrasacral (cauda equina and peripheral nerves) Lesion (CEPNL) is a neurological lesion affecting the cauda equina and/or peripheral nerves. **NLUTD** show acontractile detrusor and/or SUI may be present. In diabetic neuropathy, detrusor overactivity can be seen in combination with the above. The peripheral nerves and the lower spinal centres are often grouped under the term "lower motor neurones", as damage to these structures causes loss of contractile function.

Neurologists summarize this type of lesion in the term "subsacral lesions". With lesions in the conus most probably the nuclei for the pelvic nerves are destroyed, causing decentralisation with an areflexic (acontractile) detrusor and, once the Onuf nucleus is also involved, a flaccid sphincter and pelvic floor paresis is present. In regard to sensitivity it may be that some afferent pathways through the hypogastric nerves preserve the possibility to feel pain and slight sensation of bladder filling. With extensive autonomic damage (including nuclei of the hypogastric nerves Th10-L2) the bladder neck remains open as it is typically seen Multiple in System Atrophy (MSA).

11.2 Classification Based on Urodynamic and Clinical Findings

Madersbacher et al. [4] have developed a classification based on urodynamic and clinical findings and presented eight main types of lower urinary tract dysfunction. This system, focusing on the motor side only, is easy to understand,

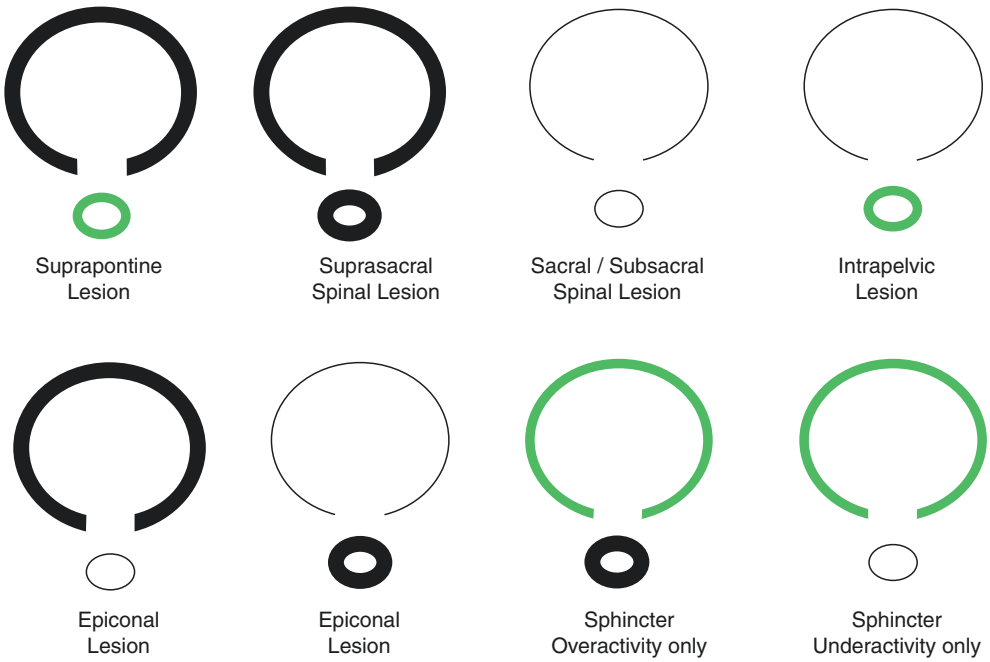

Fig. 11.2 Patterns of Neurogenic Detrusor-Sphincter Dysfunction [4]

explains the nature of the dysfunction and can be accurately characterised using urodynamics and clinical findings. It does not distinguish between complete and incomplete lesions.

Looking on these eight types of neurogenic LUT dysfunction (see Fig. 11.2) one has to consider that different etiologies may induce the same pathophysiologic pattern of the LUT, and that the same urodynamic pattern can cause different clinical implications. On the other side the same etiology may cause different patterns as with patients with myelomeningocele: 43% with overactive active detrusor and sphincter, 33% with underactivity of detrusor and sphincter, 11% with overactive detrusor and underactive sphincter and 13% with underactive detrusor and overactive sphincter. Moreover, these patterns have to a certain extent prognostic value regarding the risk for the upper urinary tract damage, the achievement of continence and the therapeutic measures to achieve these goals [5]. On the other side one also has to consider that the clinical implications of a certain urodynamic pattern may depend on the underlying aetiology: e.g. the risk for upper urinary tract damage with a spinal reflex bladder is much higher compared to a spinal reflex bladder due to multiple sclerosis.

11.3 The SALE-Classification

Only recently Powell [6] proposed a new step in classification of the neurogenic bladder: the SALE-classification (SALE = stratified by anatomic location and etiology). This classification is based on seven categories, each having a neurological defined anatomic location. They also include the bowel dysfunction aspects and should describe a patient suffering from neurogenic bladder and simultaneously inform the most appropriate treatment, follow-up regime and long-term prognosis. It is more a description of diseases due to lesions within the nervous system (central nervous system and peripheral nerves), including a short but precise characterisation of symptoms, urodynamic diagnosis and also therapeutic recommendations. Prescribing suprapontine neurological disorders they are broken down to neurogenic bladder with cerebro-vascular accident, with traumatic brain injury, with normal pressure hydrocephalus, cerebral palsy, Parkinson Disease (mentioning also MSA), under the heading of pontine neurological disorders, brain tumours and cerebellar ataxia syndromes are mentioned.

11.3.1 Conclusion

In conclusion a very specific type of disorder will be found in every single patient. The current classification systems serve as a frame work, since it is not possible to map all lesions and its consequences of every patient in one classification. There is a strong desire to be able to limit one's observations with respect to structure and functionality to a reasonable number.

Moreover, it is well known that neurogenic LUT disorders are not a static phenomenon but they may change over time due to secondary morphologic and functional changes.

Therefore follow-up and re-evaluation may be necessary in order to proceed with the correct therapy [7].

In the future more information may be obtained by using biomarkers as urinary nerve growth factor (NGF) and urinary brain-derived neurotrophic factor (BDNF) to the present classification.

So far none of the classifications really is ideal and comprise all aspects to classify the patient combing the level of the neurological lesion, its effect on lower urinary tract, the risk factors, which are involved with a specific type of lesion due to a specific aetiology and the prognosis (e.g. spinal DO caused by posttraumatic is usually much more aggressive than one due to multiple sclerosis), therefore the risk for upper urinary tract deterioration is higher with a posttraumatic lesion compared with multiple sclerosis.

11.4 Terminology of Neurogenic LUT Dysfunction

In 2002 the Standardisation Subcommittee of the International Continence Society published an article on the "Standardisation of Terminology of LUT function [8]. The definitions were written to be compatible with the WHO publication ICIDH-2 (International Classification of Functioning, Disability and Health) published in 2001 and the ICD-10, the International Classification of Diseases. This report restates the ICS principle that symptoms, signs and conditions are separate categories, and adds a category of urodynamic observations [9]. Harmonization in terminology was needed because different terms for one and the same condition were used in the literature, e.g. reflex bladder, automatic bladder, normal cord bladder, spinal reflex bladder were used to characterize neurogenic spinal detrusor overactivity. Therefore also some terms often used in Neuro-Urology are addressed in this report: The term "Neurogenic Bladder" has been replaced by "**Neurogenic Lower Urinary Tract Dysfunction" NLUTD**, to include all anatomical structure and physiological processes involved in this condition. Several new NLUTD definitions have been proposed, including symptoms, signs, urodynamic observations and definitions of clinical diagnoses and treatment. We are presenting here only few new definitions specifically related to NLUTD. Several symptoms are specific for NLUTD because of the sensory or motor impairments. Some of the patients may have **abnormal sensation** which is awareness of sensation in the bladder, urethra or pelvis, described with words like "tingling", "burning", or "electric shock". Some individuals may report **non-specific bladder awareness** with no specific bladder sensation, but may perceive e.g. abdominal fullness, vegetative symptoms, urethral sensations or spasticity as bladder filling awareness or a sign of bladder fullness.

Impaired cognition urinary incontinence is a complaint of periodic urinary incontinence that the individual with cognitive impairment reports to have occurred without being aware of it. **Impaired mobility urinary incontinence** is the complaint of inability to reach the toilet on time for voiding because of physical or medical disability. This inability includes (any combination of) the individual's physical as well as social causes or reasons. Other signs or symptoms of LUTD should not be present, or should be reported by the professional (as primary or as accessory) (e.g. 'Urgency urinary incontinence' with 'mobility impairment'; or 'Mobility impairment urinary incontinence' with 'stress urinary incontinence'. **Neurogenic overactive bladder** is characterized by urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia in the setting of a clinically relevant neurologic disorder with at least partially preserved sensation. These symptom combinations in case of preserved sensation, are suggestive of urodynamically demonstrable detrusor overactivity, but can be due to other forms of LUTD. These terms can be used if there is no proven infection or other obvious non neurological disease. Voiding dysregulation is urination in situations which are generally regarded as socially inappropriate, such as while still fully dressed, or in a public setting away from toilet facilities.

A lot of new definitions relate to urodynamic observations. Neurogenic detrusor overactivity has been already previously defined by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked in the setting of a clinically relevant neurologic disease. Provoked contraction may be elicited by cough, change of position etc., or by urethral sphincter to bladder reflex. Specific types of neurogenic detrusor dysfunctions include old and new definitions. **Phasic detrusor overactivity** and **Terminal detrusor overactivity** has been already previously published.

The new definitions include:

- **Sustained detrusor overactivity**—is defined is as a continuous detrusor contraction without returning to the detrusor resting pressure (Fig. 11.3).
- **Compound detrusor contraction**—is defined as a phasic detrusor contraction with a subsequent increase in detrusor and base pressure with each subsequent contraction.
- **High pressure detrusor overactivity**—is defined as a phasic, terminal, sustained or compound high maximal detrusor overactivity with the high detrusor pressure perceived by

investigator to be potentially detrimental to the patient's renal function and/or health and the value should be defined in the report (Fig. 11.4).

- **Neurogenic Detrusor Overactivity Incontinence**—is incontinence due to involuntary neurogenic detrusor overactivity. Incontinence can occur with or without any sensation of urgency or awareness.
- **Detrusor Overactivity Leak Point Pressure (DOLPP)**—is defined as the lowest detrusor pressure rise with detrusor overactivity at which urine leakage first occurs in the absence of voluntary detrusor contraction or increased abdominal pressure (Fig. 11.5).

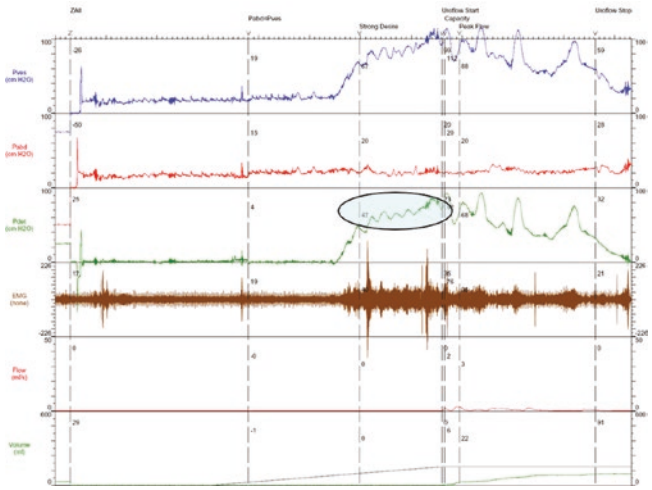

Fig. 11.3 Sustained and high detrusor overactivity

Very often patients with NLUTD and DO empty bladder spontaneously.

Balanced bladder emptying is a bladder emptying with physiological detrusor pressure and low residual as perceived by the investigator, and should be defined in the report. In contrast **Initiated reflex bladder emptying** is an artificially elicited LUT reflex comprised of various manoeuvres (exogenous stimuli) performed by the patient or the therapist, resulting in complete or incomplete bladder emptying. Spontaneous reflex bladder emptying is termed **Detrusor Overactivity Incontinence.**

Several sphincter dysfunctions are typical for NLUTD.

Detrusor-Sphincter Dyssynergia (DSD): describes a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. Occasionally flow may be prevented altogether. Neurological disease that impairs the ability of the PMC or its pathways to co-ordinate function of the LUT spinal centres, leading to detrusor contraction against a contracting outlet. Detrusor sphincter dyssynergia typically occurs in patients with a supra-sacral lesion, and is uncommon in lesions of the lower cord. DSD is responsible for bladder outlet obstruction and occasionally flow may be prevented altogether (Fig. 11.6).

Delayed relaxation of the urethral sphincter is characterized by impaired and hindered relaxation of the sphincter during voiding attempt resulting in delay of urine flow. This

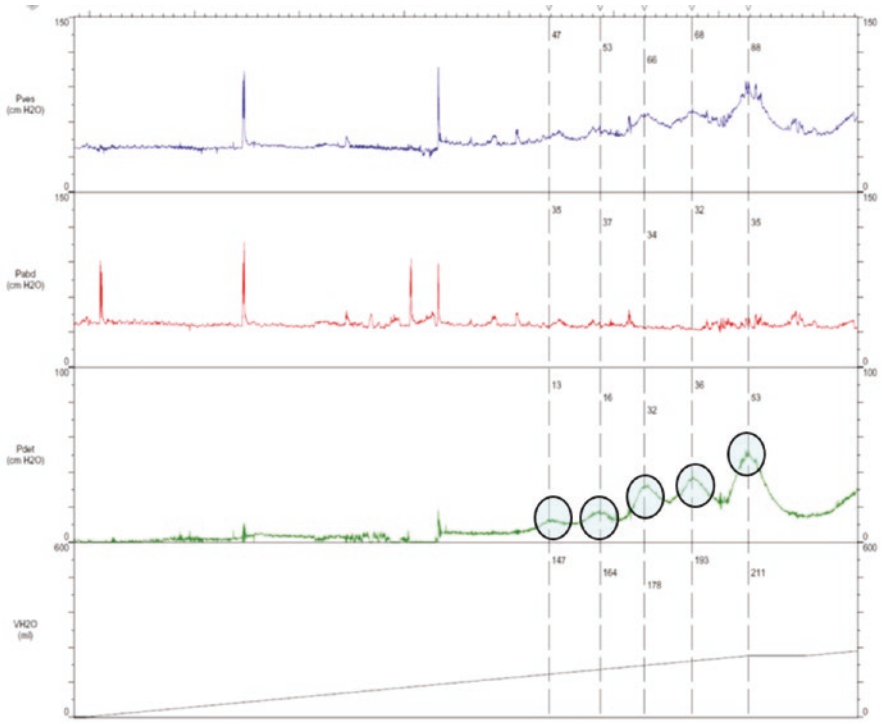

Fig. 11.4 Compound detrusor overactivity

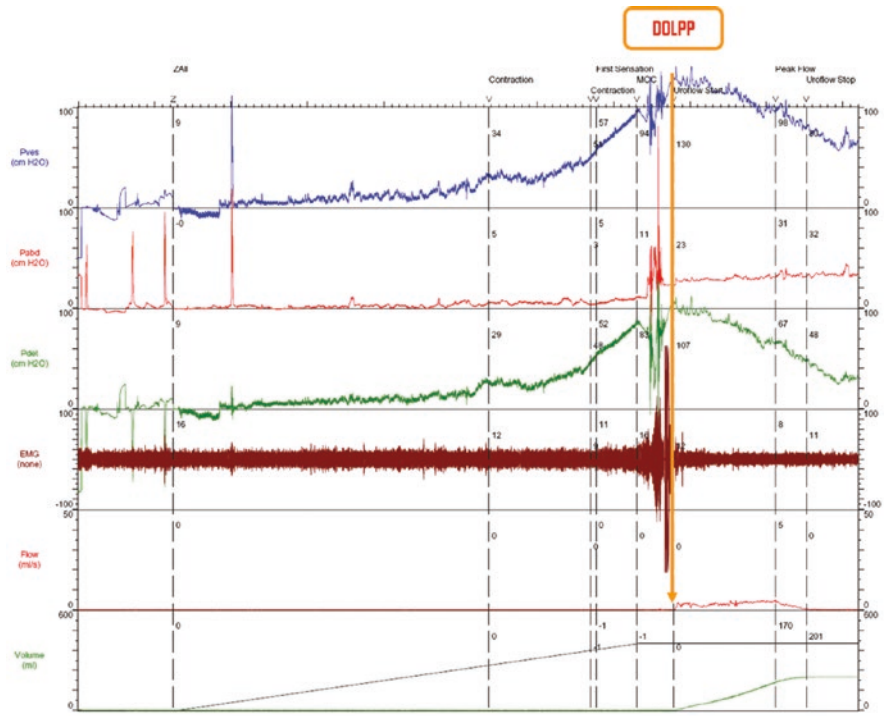

Fig. 11.5 Detrusor Overactivity Leak Point Pressure

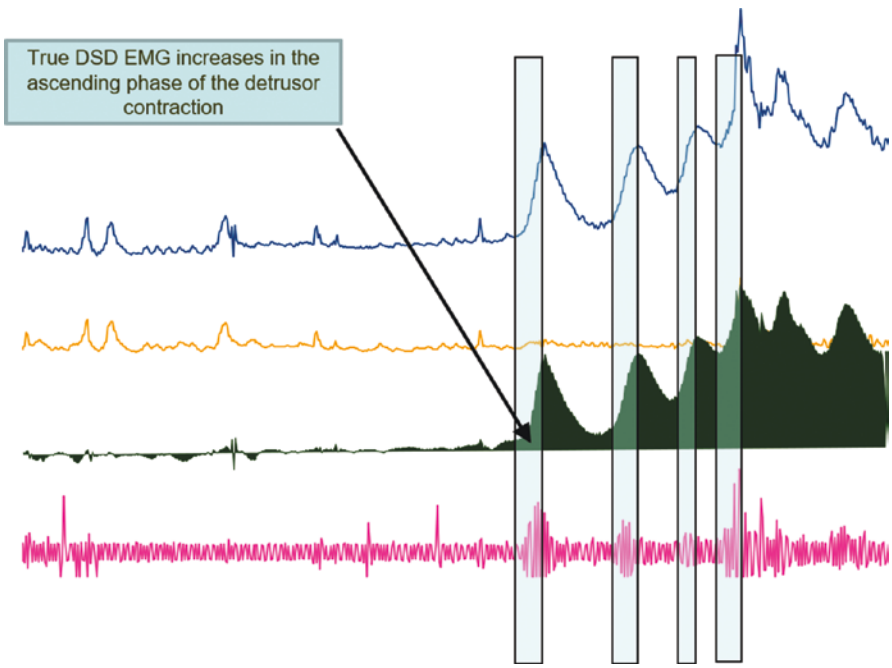

Fig. 11.6 Detrusor Sphincter Dyssynergia

can occur in some patients with Parkinson's disease or muscular dystrophy.

For the complete terminology document please refer to Gajewski et al. [9]. It is important to use proper definition in the clinical practice and research since this will improve communication and clarify patient status which consequently improve outcomes of our management of NLUTD.

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Part VII

Diagnosis and Evaluation

Patient History

12

Helmut Madersbacher

12.1 Overview

Diagnostic methods for neurologic LUT dysfunction are not very different from what is done in non-neurologic patients. Those patients with known neurologic disease often need evaluation to exclude or to prove neurogenic bladder, not only, when symptoms are already present, but as a standard diagnostic approach, if neurogenic lower urinary tract dysfunction (NLUTD) has a high prevalence in this disease. LUT problems in neurologic patients are not necessarily related to the neurologic pathology, comorbidities as prostate pathology or pelvic organ prolapse might cause or contribute to the symptoms. Extensive diagnostic work-up may be necessary to tailor an individual treatment. This may not be needed in every patient, when taking into account bad mental or physical condition as well as limited life expectancy.

12.2 Current Urinary Symptoms

It makes sense to start by questioning current urinary symptoms, as this is what patients expect. Patients should be asked for storage and voiding symptoms. Even when assessed carefully, at the time of the first visit the interpretation may be difficult in patients with neurologic disease.

12.2.1 Storage Symptoms

Regarding storage symptoms, urgency, frequency and nocturia as well as incontinence should be questioned. Moreover, in establishing exact data on micturition frequency and voided volumes a voiding diary (see below) is necessary. Urinary frequency can be caused by detrusor overactivity, related or no related to the neurological disease, but also reduced bladder capacity, polyuria, post-void residual urine, inflammatory bladder conditions, bladder tumour, stone formations or urinary infection are possible reasons. Individuals with NLUTD may not be accurate in determining, whether they have had a UTI based on classical symptoms, sometimes it is the smelly urine or an increase of autonomic dysreflexia symptoms which indicate UTI [1].

Incontinence can be of the stress-, urge-, mixed or overflow-type and may be neurogenic or due to comorbidities.

Stress incontinence occurs with increase of intraabdominal pressure and is mostly associated with physical activities, coughing, sneezing, straining, and is related to pelvic floor hypermobility or intrinsic sphincter weakness.

Urge incontinence with the key symptom of a sudden urge to void without pre-warning is considered to be due to detrusor overactivity, loss of compliance or increased bladder sensation. Typical symptoms include a sudden uncontrollable urge to urinate, night time leakage episodes and sometimes leakage during intercourse.

Overflow incontinence is characterised by constant low grade dribbling, often combined with recurrent urinary infections. The reason is either a detrusor failure or severe outlet obstruction.

Also ureteral ectopy, fistula formation and even bladder neck erosion or a scarred urethra may be the reason for incontinence.

Other important questions are: Is there a desire to void? Is there a sensation of "micturition is imminent"?

- Is there a desire to void?
  It depends on the presence and function of mechanoreceptors in the detrusor and its afferent nerve supply, which courses along the pelvic nerves, the lateral columns of the spinal cord towards the brain. If the pelvic nerves or the sacral segments are non-functioning, e.g. as it occurs with low sacral cord and/or cauda equina lesions, the desire to

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_12

void is absent. However, a sensation of suprapubic fullness remains present as long as the cord lesion is below the tenth thoracic segment with preservation of afferent fibres from the gut/peritoneum. If the level of a cord lesion is close to the sixth thoracic segment this sensation of fullness is less localised and experienced as a vague abdominal distension. Therefore when asking for sensation in the lower urinary tract, specifically for the urge to void, sometimes patients are unable to distinguish between urge and sensation of bladder fullness. The sensation of bladder fullness is also caused by distension of the peritoneum covering the bladder and is present even when the bladder afferents are damaged. If a patient says "Yes, I feel the urge to void." the additional question "Is it the same as before?" may be helpful for differential diagnosis.

- Is there a sensation of "micturition is imminent"?
  This sensation is composed of the desire to void and the proprioception of the pelvic musculature. It is conducted by pelvic and pudendal nerves and by the lateral and posterior columns.

12.2.2 Voiding Symptoms

Voiding symptoms, urinary hesitancy, straining, and loss of stream, interrupted urine flow (staccato type of voiding may indicate detrusor-sphincter-dyssynergia) are an indication for urodynamic (UD) testing. Also excessive straining is not specific. It could be caused by detrusor weakness/acontractility or/and bladder outflow obstruction and deserves UD testing for differential diagnosis. The same is true for significant post-void residual urine.

Other important questions are:

- How is the initiation of urination achieved? Is it done in a normal position, precipitously, reflexly or by straining or Credé pressure?
  Precipitate micturition is the result of inhibited voiding contractions in patients with partial suprasacral lesions anywhere along the neuraxis. Reflex micturition occurs in patients with complete suprasacral lesions. Micturition by abdominal pressure, whether through strain or with suprapubic manual pressure (Credé), usually indicates a sacral or subsacral lesion, however, also patients with functional or structural outflow obstruction may show this type of voiding. Only urodynamics are able to distinguish between these two conditions.
- Is there a sensation of "micturition in progress" or of "urine is passing"?
  Both are a composite sensation consisting of proprioception from the relaxing striated pelvic floor muscle and of extroception, thermal and maybe tactile from the urethral mucosa.
- Is there relief after voiding?
  This simple question can give information to the extent of the lesion, whether it is complete or incomplete.
- Are there associated sensations during storage and/or voiding?
  Among these are symptoms of autonomic dysreflexia which occur not only with a complete thoracic lesion above D6, but also with incomplete lesions.

The occurrence of new onset urinary symptoms, after a period of stability, in a neurogenic patient could reflect a new process requiring repeating neuro-urologic evaluation.

In patients with neurogenic LUT symptoms the reliability of a symptom questionnaire is low; this is true for storage as well as for voiding symptoms.

A bladder diary provides more precise information on the number of voids (day and night), the sensation at each void, volumes voided, incontinence and volume/time/type of fluid intake. After years of using voiding diaries there is still no consensus and no guideline in the literature on the minimal number of days for a reliable diary. Considering the information captured and balanced against the inconvenience to the patient [2], mostly recording of 2 or 3 days is regarded as sufficient [3]. The bladder diary is not only an extremely valuable diagnostic tool, but also important for the assessment of treatment outcomes as shown by Lombardi et al. [4].

Warning signs and symptoms, that warrant early further investigation include fever, pain, haematuria, catheterisation problems, clinical infections and signs of autonomic dysreflexia.

12.3 Bowel History

The assessment of bowel function is mandatory as it may coexist with bladder dysfunction in patients with neurologic conditions due to identical innervation. Questions should target on the frequency of bowel emptying—chronic constipation is defined as less than two defecations per week—, whether there is sensation for the urge to defecate, is the patient able to differentiate between gas and faeces, how is defecation initiated. The sensation "faeces are passing" is comparable with the sensation of "urine is passing". This sensation depends on the rectal autonomic nerve supply and on the pudendal nerves which conduct proprioception of the rectal sphincter. Chronic constipation may have a significant influence on LUT function. Severe stool impaction in the rectum can cause obstructing voiding symptoms or even urinary

retention [5]. Of course also the presence of faecal and/or gas incontinence should be questioned.

12.4 Sexual History

Sexual history is important as sexual dysfunction is very common among men and women with neurological conditions.

Women may have loss of libido or may not be able to have intercourse due to vaginal pain or dryness. Sometimes also increased vaginal hyperaesthesia is present. Most prevalent conditions in spinal cord injured women are disorders of arousal and orgasm.

Men may suffer from neurogenic erectile dysfunction and/or from ejaculatory problems. Erections may be absent, present only psychogenic or only reflexely.

Ejaculation is a reflex composed of emission of sperms into the prostatic urethra and its outward expulsion by chronic contractions of the bulbocavernosus musculature. The former is effected by the sympathetic hypergastric nerves, the latter by the somatic pudendal nerves. Lumbar and sacral segments are involved in this reflex, which is more vulnerable than the erection reflex. Ejaculation may be too early or too late. Missing antegrade ejaculation may be due to bladder neck dysfunction with retrograde ejaculation, drippling ejaculation due to pelvic floor muscle weakness. Therefore the questions are: Is there an ejaculation present and if so, is it projectile or dribbling?

Orgasm is a composite experience resulting from proprioception of viscerosomatic reflex activity combined with exteroception from the skin and urethra. It is conducted by autonomic and somatic nerves.

12.5 Previous Urologic History

A history of previous lower urinary tract problems as well as of previous bladder-, prostate-, upper urinary tract surgery and operative reports of sometimes complex LUT reconstruction should be looked through carefully.

12.6 History of Neurological Disease

Many patients referred to the urologist have already a diagnosed neurological condition. They are referred to evaluate whether their LUTS are due to this neurological condition or are caused by urological comorbidities.

In those patients with an already diagnosed neurological disease the onset of neurological and urological symptoms must be clarified—acute or insidious, congenital or acquired. Unless the condition is congenital or was acquired in infancy or early childhood, an individual remembering previous sensation of micturition will recognise the deficit. One has also to keep in mind that the onset of neurologic symptoms may differ from the time when the neurological disease was diagnosed. Urological symptoms can antedate the neurological symptoms (e.g. urgency in Levy-Body Dementia), sometimes the urological symptoms occur early or together with the symptoms of a neurological disease (e.g. MSA), in others only later in the course of the disease (Morbus Alzheimer) [6].

In Idiopathic Parkinson Disease (IPD) urological symptoms and signs (urodynamics) can be found early but are more or less subclinical and do not bother the patients [7]. However, with increasing severeness of IPD by time also the urological symptoms become bothersome and need therapy. Therefore the urologist should know the prevalence of LUTS in various neurological diseases and whether the urological symptoms occur early of late in the course of the disease in order to make a correct statement, whether the urological symptoms are due to the neurological condition or to urologic comorbidities.

Also in patients with a presumingly fixed neurological condition, e.g. after spinal cord trauma or with myelomeningocele, one has to realise that these conditions are not static, but may change over time due to morphologic and functional changes within the LUT [8]. Therefore recent changes of the neurological condition—often motor and sensory function—must be directly questioned.

Persistent urological symptoms, e.g. after stroke, are of prognostic importance, several studies could show that ongoing incontinence is an ominous sign [9].

With an increasing number of elderly patients in our population intravertebral disc prolapse or vertebral stenosis may cause LUT symptoms. Therefore questions, whether low back pain, perineal paraesthesia, lower extremity weakness and decrease of sexual function are present as symptoms of a cauda equina syndrome. Patients should also be evaluated about diabetes mellitus, previous herpes zoster or alcohol abuse as these condition may cause a peripheral neuropathy, especially affecting the afferent nerves. Patients reporting previous extensive pelvic surgery—radical hysterectomy, abdomino-perineal resection or radical prostatectomy—may suffer from peripheral, mostly incomplete bladder innervation damage due to an iatrogenic injury to the pelvic plexus, the same is true after pelvic radiation.

12.7 Evaluation of Current Medical Treatment

First line medication for symptoms of OAB/neurogenic detrusor overactivity are antimuscarinics, causing anticholinergic side effects. But also many commonly prescribed medicaments, especially for the elderly, have anticholinergic properties. More than half of the 25 most frequently prescribed medicaments for elderly people have such effects. Proper evaluation and adequate knowledge can help to prevent side effects caused by increasing anticholinergic serum activity with antimuscarinics (AM) [4], Table 12.1 [10].

Cholinesterase inhibitors, prescribed by the neurologist as first line therapy for memory problems, may cause also peripheral effects, thus inducing or increasing urgency. Moreover, they may interact with AM, given for symptoms of the overactive bladder by the urologist, when using AM which pass the blood-brain-barrier and/or are bound to the M1-receptors in the brain responsible for cognition: AM can block the M1-receptors so that cholinesterase inhibitors become ineffective with deterioration of cognition as consequence. Morphine, a third-line treatment for PD patients, may cause detrusor weakness, ending up in urinary retention. Typically also medicaments with either alpha-receptor agonistic or alpha-antagonistic properties can affect the bladder outlet and may either reduce or increase incontinence or may increase or reduce obstructive symptoms. Therefore the list of medicaments the patient is taking has to be reviewed carefully.

Table 12.1 Commonly prescribed drugs with anticholinergic effects [10]

Of 25 drugs commonly prescribed to older patients, 14 produced detectable anticholinergic effects		
Ranitidine	Theophylline	Cimetidine
Codeine	Nifedipine	Furosemide
Dipyramidole	Digoxin	Captopril
Warfarin	Lanoxin	Dyazide
Isosorbide	Prednisolone	

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Physical Examination

13

Helmut Madersbacher

The general impression of the patient's physical and mental possibilities is relevant to the choice of investigation and treatment. Severe impaired mobility, extreme spasticity, severe mental disorder or general weakness are all important in this respect [1].

The physical examination should evaluate the lower abdomen, the external genital organs and perineal skin. The neuro-urological examination should comprise (1) sensitivity testing in the sacral dermatomes, (2) rectal examination and (3) reflex testing.

13.1 Sacral Sensitivity Testing

Sensitivity testing evaluates the sensation for pain and touch in the sacral dermatoms. The patient should be in lithotomy position to have access to the lower sacral segments S3, S4 and S5 (see Fig. 13.1).

Which information is provided by testing the sensitivity in the sacral dermatomes, why to check for pain (pin-prick) and touch sensation separately? The spinal pain pathways (Tractus spinothalamicus) are located in the lateral columns and the bladder pathways (incl. those for the urge to void) are nearby. The bladder pathways for touch and pressure sensation, however (incl. those for fullness of the bladder), are located in the posterior columns (see Fig. 13.2).

Therefore in incomplete lesions and depending on its location the urge to void may be preserved even when the sensation for touch and pressure is missing and vice versa. A good exampl is the anterior spinal cord syndrome with which the blood supply to the anterior portion of the spinal cord is interrupted. The posterior portion including the posterior columns remains functionally intact, therefore, these patients do not feel the urge to void but they have still sensation of bladder fullness. To interpret correctly the findings of sacral sensitivity testing and the information given by the patient in regards to feeling of urge and bladder fullness, one has to consider the anatomical situation: stimuli from the sacral dermatomes are conveyed to the spinal cord via afferent fibres in the sacral roots. The afferent fibres from the bladder join these sacral roots before they enter the sacrum. Missing sensations in the sacral dermatomes indicate that the relevant afferent nerves are damaged either in the periphery or in the spinal cord. Sacral sensation may be present, but bladder sensation missing, when the damage to the bladder innervation is in the periphery distal from the point where the afferent nerves from the bladder enter the sacral nerves. Therefore, typically for patients with peripheral bladder denervation is that the sensation for the urge and bladder fullness is missing despite normal sensation for pain and touch in the sacral dermatomes (see Fig. 13.3).

Moreover, the absence of pin-prick sensation predicts poor bladder recovery in spinal cord injured patients [2].

13.2 Rectal Examination

Rectal examination in patients with neurogenic LUT dysfunction should not just focus in men on the prostate and whether there is any abnormality in the rectum (tumour) but must comprise in men and women the configuration of the anus (normal, patulous), the anal sphincter tone (normal, spastic, flaccid) and the ability of the patient to contract and to relax voluntarily the external striated anal sphincter. Voluntary contraction and relaxation means that the patient is able to activate the relevant cortical areas, that the pathways in the pyramidal tract to the nuclei of the pudendal nerve in the anterior horn of sacral cord as well as the pudendal nerve are preserved and that the motor function is intact. Preserved ability for voluntary contraction and relaxation is a good prognostic sign to achieve continence with bladder retraining programmes. The ability to contract the anal sphincter is

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_13

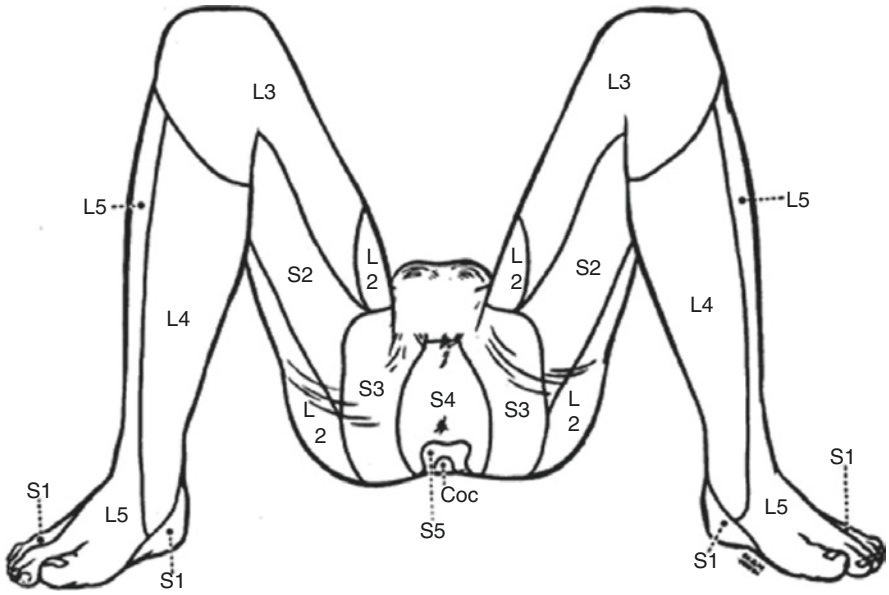

Fig. 13.1 Sacral dermatomes

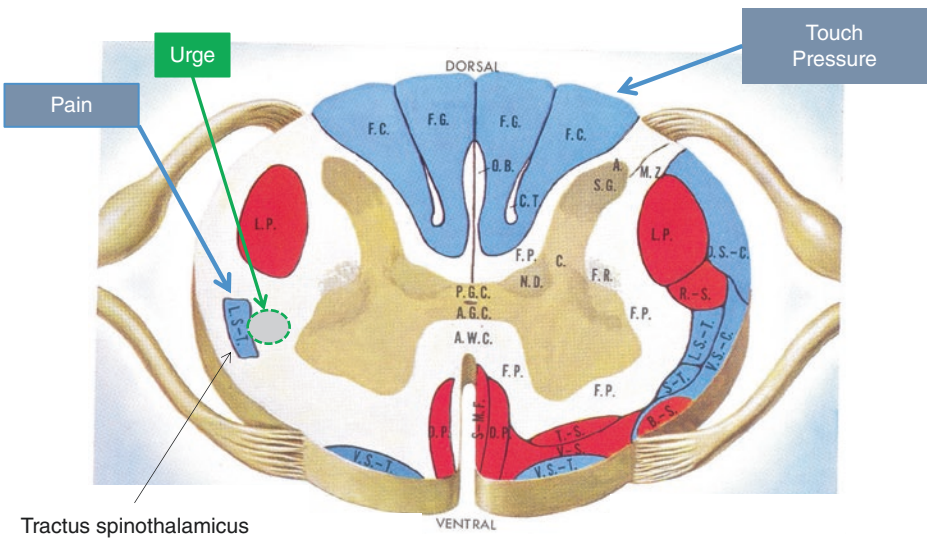

Fig. 13.2 Sensitivity for touch and in the sacral dermatomes (Netter amended by Madersbacher)

important for the management of urgency: it has been be shown with functional MRI studies that repeated contractions of the pelvic floor activate areas in the basal ganglia (bilateral putamen) which are considered to be important for detrusor suppression [3]. Rectal examination should also detect stool impaction due to neurogenic bowel dysfunction which can interfere with micturition simply by mechanical pressure to the bladder neck and the posterior urethra.

13.3 Reflex Testing

Important reflexes in the lower spinal cord are the cremasteric reflex (L1/L2), the knee reflex (L2-L4), the ankle reflex (L5-S2) and especially important for the neuro-urologist the bulbocavernosus (L5-S5) and the anal reflex (S4-S5).

The bulbocavernosus reflex (BC) test consisted originally of a perineally palpated contraction of the bulbo- and ischiocavernosus muscle in response to squeezing to the glans penis. The method was modified by testing the response of the external anal sphincter to the same stimulus. In females the BC reflex is elicited by touching slightly, squeezing or gently tapping the glans clitoritis. The BC reflex returns within a few hours after spinal cord injury in contrast to the return of other reflex activity. The BC reflex may be reduced or even absent in older individuals but is present in at least 70% of males with an intact neuraxis. Severe spasticity may overfacilitate the rectal sphincter so that no additional response can be elicited. There is no doubt that the efferent limb of the BC is in the

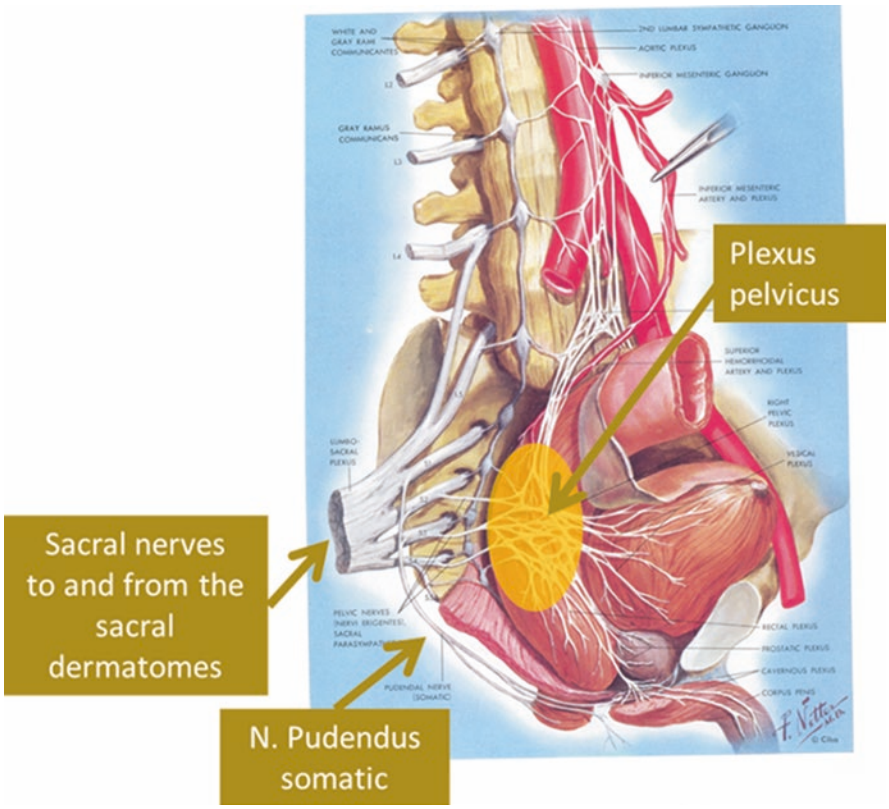

Fig. 13.3 With peripheral bladder denervation the sacral sensitivity testing shows no ab normality (Netter, amended by Madersbacher)

anterior sacral roots, the course of the afferent limb is not yet clear as complete posterior rhizotomy below D10 did not abolish the reflex [4]. For the BC reflex testing the patient should be relaxed in lithotomy position, with the rectum empty or minimally filled. In spinal cord injured patients with a suprasacral spinal cord lesion positive BC reflex correlates with detrusor-sphincter/bladder neck-dyssynergia. Moreover presence/absence of BC and anal reflexes correlate significantly with detrusor and striated sphincter reflexia/areflexia. A negative BC reflex indicates a defect in the sacral reflex arc either on the efferent side of the pudendal nerve, in the spinal cord segments L5-S5 or on the afferent side [5].

BC and anal reflex correlate well with NLUTD in some types of neuropathy, such as single level traumatic spinal cord lesion, but less in other types, e.g. meningomyelocele or combined traumatic spinal cord lesions [6, 7].

The anal reflex consists of a visible external rectal sphincter response to perineal skin stimulation by pin-prick. It usually parallels the findings of the BC reflex.

The cough reflex comprises a contraction of the external rectal sphincter in response to deep inspiration or coughing. It is a spinal reflex which depends on volitional innervation of the abdominal musculature extending from D6-L1. As long as one segment remains under volitional control the cough reflex is positive. The cough reflex normally parallels the BC reflex.

In summary, with possibly a few exceptions, neurogenic lower urinary tract dysfunction reflects the involvement of the neurological disease in the innervation of the lower urinary tract but the findings are mostly not diagnostic for a specific neurological condition.

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General Laboratory Tests

14

Nuno Grilo and Brigitte Schurch

14.1 Urine Tests

14.1.1 Dipstick Analysis

Urine dipstick is a widely used and easily available test of screening for urinary tract infections (UTI). Its ability of detection of an UTI relies in two parameters, the presence of leukocytes and nitrites in the examined urine.

A meta-analysis conducted by Deville et al. investigated the diagnostic accuracy of the urine dipstick test in detecting significant bacteriuria or urinary tract infection. Overall, the sensitivity for nitrites was low (45–60%) but specificity was fairly high, ranging from 85 to 98%. However, leukocyte-esterase test sensitivity seems to be higher than nitrite test (48–86%) with on the other hand a lower specificity (17–93%). Combination of both tests seems to increase sensitivity (66–88%) and increases predictive value of a negative test [1].

Significant bacteriuria being such a prevalent condition in the neuro-urology population, differentiating it from an UTI is key, even more regarding the rapidly increasing antibiotic resistance rates. Unfortunately, when applied to SCI patients, dipstick test does not help in the decision of when to start antibiotherapy, as it fails to differentiate between these two conditions. On the other hand, due to its excellent negative predictive value, it is a useful test to exclude urinary infection and more over to assess response to antibiotic treatment [2].

14.1.2 Urine Culture

Urine culture is the gold standard to diagnose urinary infection and significant bacteriuria. In the absence of symptoms, a bacterial growth of $\geq 10^5$ cfu/mL in two consecutive samples in women and in a single mid-stream sample in men diagnoses significant bacteriuria [3]. A bacterial count as low as 10^2 cfu/mL seems to be a threshold with high sensitivity and acceptable specificity to define significant bacteriuria in patients under CIC [4]. On the other hand, a urinary infection is usually diagnosed in presence of de novo lower urinary tract symptoms (LUTS) and a positive urine culture.

The difficulty in differentiating significant bacteriuria from UTI lies in the fact that assessment of LUTS symptoms is particularly difficult in neuro-urological patients, as these can be completely absent, or be chronically present due to neurogenic bladder dysfunction [5]. In presence of de novo or exacerbation of LUTS, a urine culture is advised in order to guide treatment. A highly suspicious approach should also be taken in the presence of fever, malaise and other general symptoms, neurological deterioration or malodorous/turbid urine. Phe et al. have proposed a flow-chart to help guiding the diagnosis and management of UTI in multiple sclerosis patients (Fig. 14.1). A similar procedure could also probably be applied to SCI patients.

14.1.3 Urine Cytology

Urine cytology has an overall sensitivity of 55% (95% CI 48–62) and specificity of 94% (95% CI 90–96) [6]. Urinary cytology has indeed a high sensitivity in high-grade tumours (84%), but a very low one in low-grade tumours (16%), therefore it cannot be used as a sole test to assess the presence of a bladder tumour, but is mainly useful when coupled with cystoscopy [7].

14.2 Blood Tests

14.2.1 Renal Function Tests

These tests are discussed in the renal function evaluation chapter (Chap. 21).

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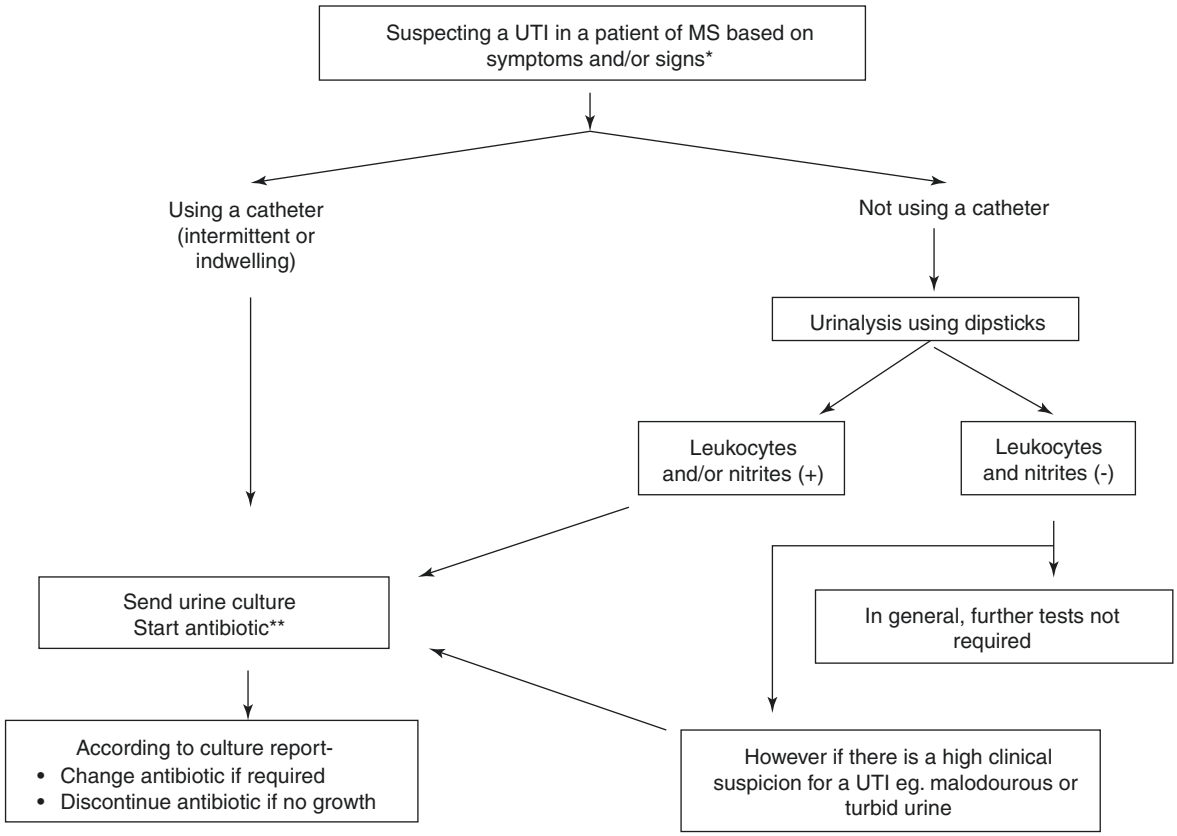
L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_14



**Symptoms and signs* of a UTI*

- *Local: suprapubic pain, flank pain, recent worsening of urinary urgency/frequency and/or incontinence, leakage between intermittent self-catheterization, catheter blockage, cloudy urine with increased/foul odour, hematuria*
- *General: unwell, fever, chill, back or abdominal discomfort, reduced appetite, lethargy, deterioration of preexisting neurological condition, eg. mobility, spasticity*

***The choice of empirical antibiotic depends upon antimicrobial policy*
UTI: urinary tract infection

Fig. 14.1 A flow-chart to help guiding the diagnosis and management of UTI in multiple sclerosis patients

14.2.2 PSA

Despite its controversial character, prostate cancer screening remains a recommendation in patients at risk:

- >50 years
- >45 years with a family history of prostate cancer or African-Americans

It should be offered to well informed patients, with good performance status and a life-expectancy of at least 10–15 years. Prostate cancer screening relies in prostate-specific antigen (PSA) levels coupled with digital rectal examination. PSA is an organ specific serum marker, but not cancer-specific, as it can be increased in other conditions as prostatic hypertrophy and prostatitis [8]. With the improvement in management of spinal cord injury patients, a significant life expectancy increase was achieved in this subset of the patients to such extent, that their life expectancy nowadays doesn't differ from normal population [9]. Prostate cancer screening should therefore be offered to SCI patients with same criteria than for general population. A milestone in the interpretation of PSA in the neuro-urology patients is the fact that these are a lot more prone not only to urethral manipulation but also urinary tract infections, which may impact PSA levels. Indeed, both acute urinary retention and the presence of an indwelling catheter or urinary infection are associated with an increase of PSA levels, but it remains unclear to which extent [10–13].

More recently, also the impact of clean intermittent catheterization (CIC) has been studied by Torricelli et al. It seems that CIC may be associated with more than a twofold

increase of PSA level. Caution is advised, in the interpretation of this tumor marker in this subset of neuro-urological patients [14].

14.2.3 ADH

Nocturnal polyuria is a frequent condition in spinal cord injury patients. It is not only bothersome for patients and/or caregivers, but it can even be life threatening when associated with dysreflexic crisis due to bladder overdistension during the night [15, 16]. Antidiuretic hormone (ADH) is one of the key factors of water homeostasis, and therefore an impairment of its production may result in nocturnal polyuria. As shown by Szollar et al., ADH secretion is impaired in SCI patients, with persistent low levels of this hormone throughout 24 h, without what would be an expected peak between 24 h and 4 h in the morning. This is also true for post-stroke patients. In these two groups, in presence of a nocturnal polyuria, ADH diurnal pattern should be assessed to help guiding treatment [17, 18].

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Conventional Urodynamics

15

Marcio A. Averbeck and Thomas M. Kessler

15.1 Introduction

The lower urinary tract (LUT) has its function related to the storage of urine at low pressure and the normal voiding process, which depends on the effective contraction of the detrusor and synergic relaxation of the urethral sphincter. This activity is regulated by a neural control system in the brain and spinal cord that coordinates the urinary bladder and bladder outlet [1]. Neurological diseases, e.g. spinal cord lesions, multiple sclerosis, Parkinson disease, etc., can lead to lower urinary tract dysfunction and its consequences (urinary tract infections, urinary incontinence, stone formation, renal failure, etc.).

One interesting point to observe is that lower urinary tract symptoms (LUTS) and long-term complications often do not correlate [2]. One of the most fearful complications is renal damage secondary to elevated storage pressure in the bladder [3]. In this setting, the diagnostic workup is important to establish whether the patient with neurological disease has a low or high risk of subsequent complications [1–4]. Suprasacral infrapontine spinal lesions can often cause sustained elevated storage pressure in the bladder, due to a combination of detrusor overactivity and detrusor sphincter dyssynergia. Fortunately, in most other patients with neurogenic lower urinary tract dysfunction (NLUTD), the risk of renal damage is relevantly lower [1]. Nowadays, with improved diagnostic workup and development of new treatment strategies, e.g. antimuscarinics, botulinum toxin A, bladder augmentation techniques and intermittent self-catheterization, respiratory diseases became the most frequent (21%) cause of death in patients with spinal cord injury (SCI) [5].

As urodynamics and clinical symptoms often do not correlate, asymptomatic patients can present with abnormal urodynamic findings being so far unrecognized risk factors [6]. Changes in urodynamics and subsequent damage to the LUT may antedate clinical symptoms. Therefore, comprehensive urological assessment is essential in patients with NLUTD. Treatment and intensity of follow-up examinations are based on the type of NLUTD [1].

A thorough medical history, including bladder diary, and targeted physical examination is mandatory, before any additional diagnostic investigations are planned. Early diagnosis and treatment are important to avoid irreversible changes within the LUT, both in congenital and acquired neurological diseases [1].

The diagnostic workup must be aimed to accurately evaluate the status of the detrusor and the sphincter. In these regards, Madersbacher [6] proposed a simple classification focused on therapeutic consequences. This classification describes several NLUTD on the basis of the activity/contractility of the detrusor and external urethral sphincter during the storage and voiding phase (Fig. 15.1).

Urodynamic investigation (UDI) is the gold standard to evaluate lower urinary tract function in patients with neurological diseases, especially when there is evidence or history of spinal cord injury (SCI) [1, 7]. Indeed, complete neuro-urological assessment including UDI is strongly recommended in all acute SCI patients, regardless of the ability to walk [8]. Preparation before urodynamics is described in Table 15.1.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_15

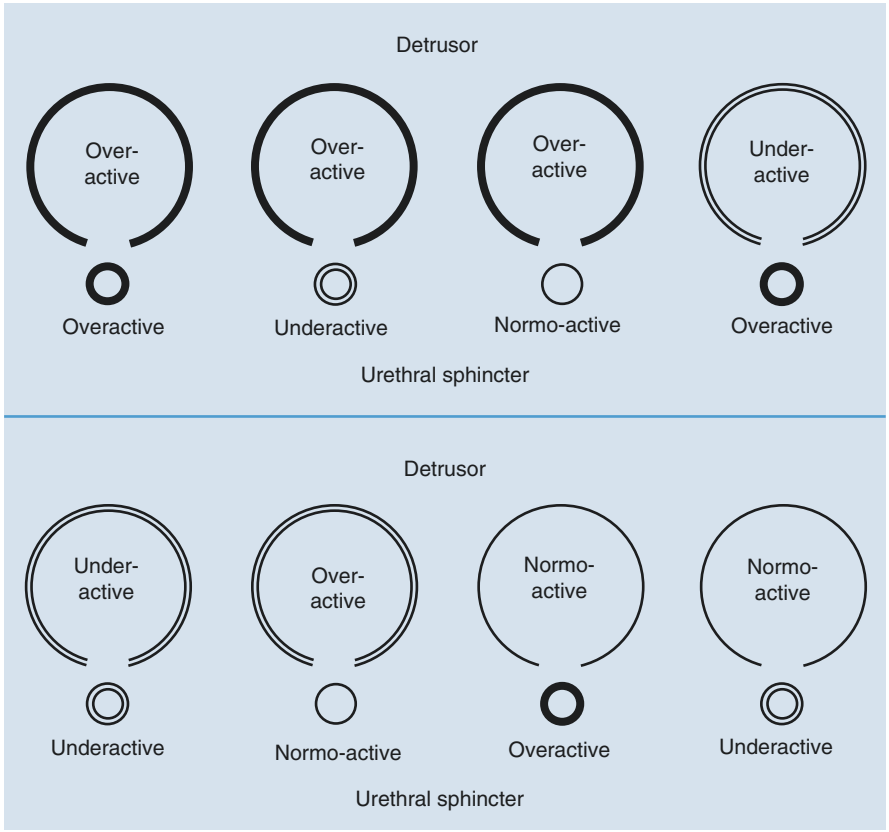

Fig. 15.1 Madersbacher classification system with typical dysfunction patterns [6]

Table 15.1 Preparation before urodynamics

Bowel management
It is recommended that the patient empties the rectum in the usual way the evening before the investigation (avoid enemas shortly before the investigation).
Medications
Drugs that influence the LUT function should be considered when interpreting the data obtained. Stopping drugs before urodynamics is generally not needed but may become relevant in special circumstances and should therefore be considered before the investigation on an individual basis depending on the questions to be answered.

15.2 Bladder Diary

Non-invasive diagnostic tools provide a first impression on the pattern of the lower urinary tract dysfunction. A 3-day-bladder diary is usually recommended before the urodynamics [9]. The bladder diary records the times of micturitions and voided volumes, incontinence episodes, pad usage and other information such as fluid intake, the degree of urgency and the degree of incontinence [10]. Additional information may include pad usage, incontinence episodes and the degree of incontinence. Episodes of urgency and sensation might also be recorded, as might be the activities performed during or immediately preceding the involuntary loss of urine [11].

15.3 Pad-Weighing Test

This is a non-invasive test that gives an estimate on the severity of urinary incontinence. The amount of urine lost over the duration of testing should be quantified, by measuring the increase in the weight of the perineal pads (weighed pre- and post-testing) [11]. To date there is no consensus on the duration (1-h test versus 24- to 48-h tests) and on protocol (provocative maneuvers vs. normal everyday activities) for patients with NLUTD.

15.4 Free Uroflowmetry

Free uroflowmetry objectively demonstrates the pattern of urine flow (low, intermittent, normal) and should be repeated two to three times before invasive urodynamics. Whenever feasible, free uroflowmetry should be done (Fig. 15.2).

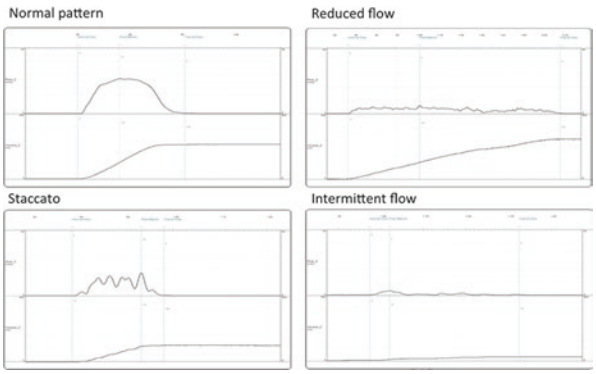

Fig. 15.2 Free uroflowmetry curves

15.5 Residual Urine

Post-void residual urine (PVR) is usually measured after a free uroflowmetry [12]. Although transurethral catheterization has been accepted as the gold standard for PVR measurements, this may cause discomfort for patients and carries a risk of urinary tract infection and trauma [13]. For these reasons, non-invasive ultrasound bladder volume measurement was implemented in clinical practice. Ultrasound bladder volume estimation can be performed in two ways; either by using real-time ultrasound to directly visualize the bladder [14] or by using a portable bladder scanner to calculate the volume automatically without directly visualizing the bladder [15, 16].

When real-time ultrasound scanning of the lower urinary tract is performed transabdominally in the transverse and sagittal planes, and the height, width, and depth of the bladder are determined. These three diameters are multiplied by a correction coefficient of 0.7, which accounts for the nonspherical shape of the bladder when it is less than completely full. This formula probably is the simplest US formula for PVR volume determination.

15.6 Filling Cystometry

Urodynamic parameters, in combination with the bladder diary and the medical history, allow for diagnosis and treatment. Special attention should be given to appropriate standardization of the urodynamic technique since this is the prerequisite for reproducible and reliable results. Hence, UDI has to be performed and reported in accordance with the standards of the International Continence Society (ICS) [17]. Any technical source of artifacts must be critically considered, and all urodynamic findings have to be reported in detail (Table 15.2).

Table 15.2 Urodynamic characteristics/findings [10]

Urodynamic observations
Intravesical pressure (cmH_2O)
Abdominal pressure (cmH_2O)
Detrusor pressure (cmH_2O)
Filling rate (mL/min)
Bladder sensation (First sensation of bladder filling, first desire to void, strong desire to void; normal, increased, reduced, absent, non-specific bladder sensation, bladder pain or urgency)
Storage
Maximum cystometric capacity (mL)
Bladder compliance (volume change divided by the change in detrusor pressure) (mL/cmH_2O)
Abdominal leak point pressure (cmH_2O)
Detrusor leak point pressure (cmH_2O)
Maximum detrusor pressure during storage phase (cmH_2O)
Voiding
Voided volume (mL)
Voiding time (s)
Maximum flow rate (mL/s)
Average flow rate (mL/s)
Maximum detrusor pressure during voiding phase (cmH_2O)
Maximum detrusor pressure at maximum flow rate (cmH_2O)
Post void residual (mL)
Urodynamic diagnosis
Detrusor function
Normal detrusor function
Detrusor overactivity
Phasic detrusor overactivity
Terminal detrusor overactivity
Detrusor overactivity incontinence
Acontractile/hypocontractile (underactive) detrusor
Bladder compliance: normal, low
Bladder capacity: normal, low, high
Stress urinary incontinence
Outlet/urethral function
Normal urethral function
Abnormal urethral function
Bladder outlet obstruction
Detrusor sphincter dyssynergia
Non-relaxing urethral sphincter obstruction

Adapted from Abrams et al., Neurourol Urodyn 2002;21:167–78

Filling cystometry is performed to assess the storage (filling) phase. A double-lumen transurethral or suprapubic (6–10 French) catheter (the catheter lubricant should be without anesthetic additive to avoid an impact on bladder sensation) is used. The bladder has to be emptied with intermittent catheterization before each UDI. A physiological filling rate (ideally, should not exceed body weight in kilograms divided by four) [18] should be used. The fill medium can be physiological saline, or a mixture of a contrast medium and saline at body temperature. A fast fill rate, non-physiological ion concentrations, and low temperature of the filling fluid may all negatively affect urodynamic results [1]. During filling, provocation tests, including coughing, change of position from supine or sitting to

standing, or hand washing, can be used to demonstrate inducible detrusor overactivity, urgency or stress, and urinary incontinence.

Bladder sensation during UDI is assessed on the basis of the volume in the bladder at the patient's first sensation of bladder filling, first desire to void, and strong desire to void. Urgency is defined as the sudden, compelling desire to void [10].

The "ice water testing" can be used to test for temperature-sensitive reflex detrusor contraction mediated by afferent C fibers. Detrusor overactivity may be demonstrated, even if there is no detrusor activity in the standard UDI, thereby helping to unmask a putatively acontractile detrusor. Since the ice water test is a non-physiological investigation that may relevantly bias subsequent UDIs, it should be performed at the end of (and not precede) more physiological standard UDIs [19].

15.7 Detrusor Leak Point Pressure (DLPP)

One of the most commonly used prognostic urodynamic parameters to predict the risk for UTT damage has been the detrusor leak point pressure (DLPP). The *International* Continence Society (ICS) defines the DLPP as the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure [10].

DLPP testing originates from observations of video-urodynamic studies of children with myelomeningocele (MMC) and urinary incontinence secondary to impaired bladder compliance. McGuire retrospectively evaluated this group of children with the aim to find predictors for upper urinary tract deterioration (UUTD). He reported ureteral dilatation on intravenous pyelogram in 81% and VUR in 68% of children with DLPP greater than 40 cmH_2O [20].

However, there is no consensus on cut-off points to be used in adults with NLUTD. Ozkan et al. [21] studied bladder histopathologic changes and detrusor leak point pressure (DLPP) as predictors for UUT deterioration in adult patients undergoing augmentation cystoplasty due to neurogenic detrusor overactivity. Full-thickness bladder biopsies were obtained for evaluation using light microscopy. The severity of detrusor fibrosis was a significant risk factor for UUT deterioration ($P = 0.036$). A DLPP of more than 75 cmH_2O has also been identified as a statistically significant risk factor ($P = 0.04$).

15.8 Abdominal Leak Point Pressure (ALPP)

Abdominal leak point pressure is the intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction [16]. This parameter is often correlated with the clinical complaint of stress urinary incontinence (SUI) and may suggest the presence of sphincter underactivity/deficiency in patients with neurological diseases. According to the ICS standardization document, the leak pressure point should be qualified according to the site of pressure measurement (rectal, vaginal or intravesical) and the method by which pressure is generated (cough or valsalva).

15.9 Pressure-Flow Study

A pressure-flow study is performed to assess the voiding (emptying) phase, and reflects the coordination between the detrusor and urethra/pelvic floor during micturition. Possible pathological findings include detrusor acontractility/underactivity and bladder outlet obstruction, including detrusor sphincter dyssynergia (DSD) and postvoid residual [17]. It has to be considered that many patients with SCI will not be able to void spontaneously; that is, maximum cystometric capacity and postvoid residual will be identical.

15.10 Electromyography (EMG) Combined with Cystometry

Electromyography (EMG) of the pelvic floor, including urethral and anal sphincter activity, is an established method for the diagnosis of bladder sphincter dysfunctions. The pelvic floor EMG is usually simultaneously measured with cystometry. Surface electrodes should be placed ventral and close to the anus. The EMG amplitude is measured in millivolts (mV) and provides a simple semi-quantitative tracing of the muscle activity over time. Surface electrodes are therefore highly vulnerable to artifacts, and the signal should be monitored throughout the measurements (e.g., by zoom tracing on the tracking software, oscilloscope, or audio signal). Urine leakage (especially in the supine position) can lead to misinterpretation of EMG findings, as fluid contact with the surface electrodes may mimic DSD (defined by the ICS as a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscles) [10].

15.11 Urethral Pressure Measurement

15.11.1 Urethral Pressure Profile (UPP)

The urethral pressure profile is a graph indicating the intraluminal pressure along the length of the urethra [10]. UPP is a technique of recording pressures along the length of the urethra with the bladder at rest. The maximal urethral closure pressure (MUCP) is the maximum urethral pressure minus intravesical pressure. The functional urethral length is the distance along the urethra in which urethral pressure exceeds bladder pressure.

According to the ICS standardization of terminology of lower urinary tract function, there are some important definitions related to the UPP:

- Urethral pressure is defined as the fluid pressure needed to just open a closed urethra;
- The urethral closure pressure profile is given by the subtraction of intravesical pressure from urethral pressure;
- Maximum urethral pressure is the maximum pressure of the measured profile;
- Maximum urethral closure pressure (MUCP) is the maximum difference between the urethral pressure and the intravesical pressure;
- Functional profile length is the length of the urethra along which the urethral pressure exceeds intravesical pressure in women;
- Pressure "transmission" ratio is the increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure.

15.11.2 Urethral Pressure Measurement

Voiding begins with a decrease in urethral pressure, followed by a detrusor contraction that increases bladder pressure and opens the urethra, resulting in urine flow. Continuous pressure measurements in the urethra during the bladder storage phase allow for observations of (smooth) muscle closure activity. However, potential artifacts may be induced by the insertion of a catheter of a certain dimension that changes the basic closure conditions of the urethra [22].

Micturitional urethral pressure profilometry, or voiding profilometry, provides a method of assessing the dynamic behavior of the lower urinary tract during voiding [23]. Simultaneous monitoring of both bladder neck and external sphincter regions in association with monitoring of detrusor activity provides information about the interactions between the detrusor, the urethral smooth muscle sphincter, and the urethral striated sphincter during a micturitional cycle. This can be achieved with a triple microtransducer catheter designed so that the two distal transducers can be positioned simultaneously in the vicinity of the bladder neck and the external sphincter regions (membranous urethra), or with a conventional fluid infusion catheter situated at a particular site in the urethra during micturition [23].

Urethral pressure measurement is not a generally agreed standard procedure in Neuro-Urology and therefore of limited value in daily neuro-urological practice.

15.12 Video-Urodynamics

15.12.1 X-Ray

Urodynamic evaluation (or 'urodynamics') is aimed at defining the pattern of (dys) function of the LUT and should reproduce the patient's urinary complaints. However, potential discrepancies between the findings of conventional urodynamics and clinical presentation are not unusual. For this reason, the idea of combining simultaneous fluoroscopy to urodynamics, with the objective of providing additional information about the anatomy and function of the LUT, has arisen [24].

After more complicated descriptions, such as 'synchronous cine-pressure-flow-cysto-urethrography' [24], the term "video-urodynamics" was introduced in 1980 to describe fluoroscopy coordinated with concurrent cystometry [25]. Video-urodynamics can be defined as a diagnostic technique based on simultaneous recording of the various urodynamic parameters with visualization of the urinary tract using fluoroscopy or ultrasound techniques [26].

Video-urodynamics requires a more complex structure, availability of expensive equipment and specialized staff. Exposure to radiation is also a limiting factor. Thus, before referring patients to video-urodynamics, it is essential to have two fundamental questions in mind: (1) Which additional information can this examination provide? (2) Which patient benefits the most from this diagnostic modality?

With broader utilization of video-urodynamics in the 1970s, it proved to be of special value in NLUTD [27, 28]. According to the guidelines of the *European Association of Urology* (EAU), video-urodynamics are the gold standard for UDI in neuro-urological disorders (1). It provides information on the anatomy of the urinary tract that can be analyzed in conjunction with the urodynamic parameters of interest in real time. In this way, artifacts and errors of interpretation

could be minimized. On the other hand, improved understanding of anatomy and function would yield more accurate diagnoses and thereby improve therapeutic decision making [29]. Video-urodynamics allow a comprehensive assessment of many parameters of interest, such as [28, 29]:

- the position of the bladder neck in relation to the pubic symphysis;
- bladder neck closure during rest and with stress;
- identification of (pseudo-) diverticula of the bladder and urethra;
- urethral opening before observed urinary leakage;
- visualization of vesico-vaginal and urethra-vaginal fistulas and vesico-ureteral and vesico-uretero-renal reflux;
- distinguishing bladder neck vs. rhabdosphincter dyssynergia (i.e. detrusor internal sphincter dyssynergia vs. detrusor external sphincter dyssynergia), and accurate localization of urethral obstruction.

The principles that guide the realization of video-urodynamics are the same as those recommended by the International Continence Society (ICS) for conventional urodynamics [17]. A double lumen (6–10 Fr) catheter is usually recommended for assessment of intravesical pressures and for infusion of sterile radiographic contrast medium. Nevertheless, there is no standardization for the fluoroscopy time during video-urodynamics. Most reports do not state dosage or exposure time and do not report the imaging protocol [28, 30–33].

Anding et al. suggested that when using video, every attempt should be made to minimize exposure based on the ALARA (as low as reasonably achievable) principal [28].

Video-urodynamics are usually indicated in clinical practice for patients with multifactorial etiology of urinary incontinence, especially for those individuals with suspected anatomical abnormalities of the lower urinary tract. Adding video to urodynamics may also provide useful information for patients with NLUTD [34], as there are some risk factors for upper urinary tract deterioration that can only be detected by this technique.

15.12.1.1 Neurogenic Lower Urinary Tract Dysfunction (NLUTD)

Video-urodynamics allow the accurate diagnosis of detrusor sphincter dysfunction (including detrusor internal or external sphincter dyssynergia, anatomical causes of infravesical obstruction, etc.) (Fig. 15.3). In addition, his technique provides important information on morphological changes of

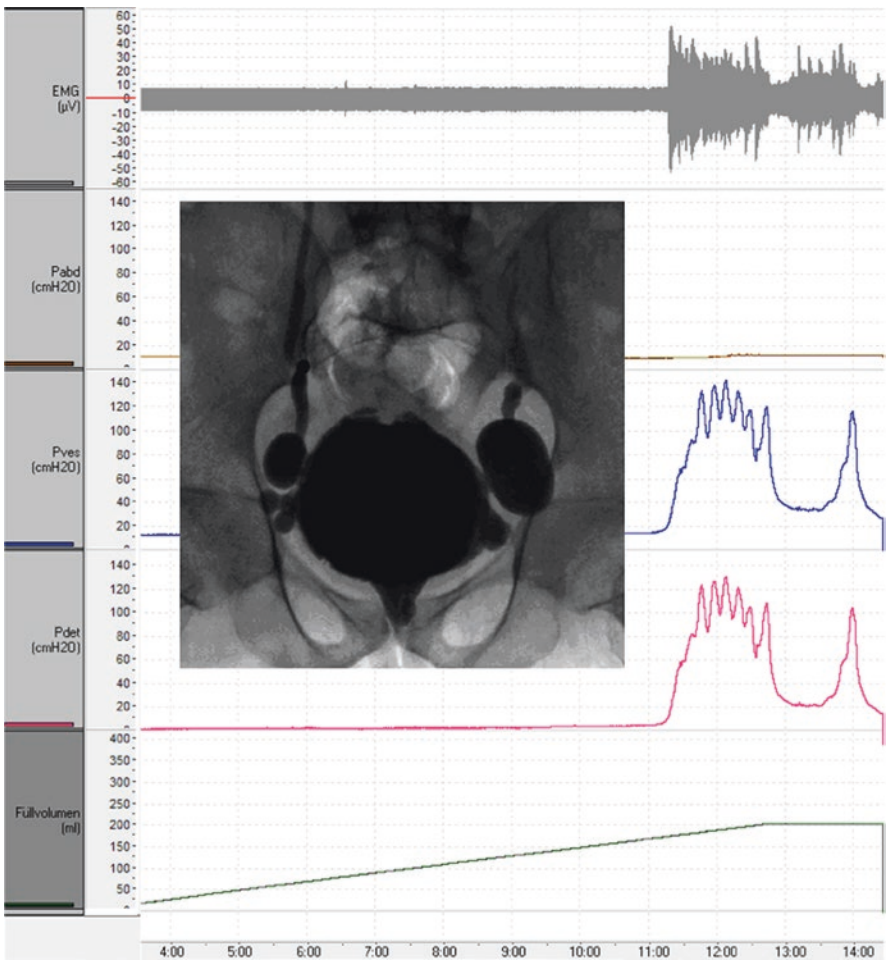

Fig. 15.3 The typical high-pressure "neurogenic bladder" with detrusor sphincter dyssynergia, (pseudo-)diverticula, trabecula, and bilateral vesico-uretero-renal reflux jeopardizing the upper urinary tract

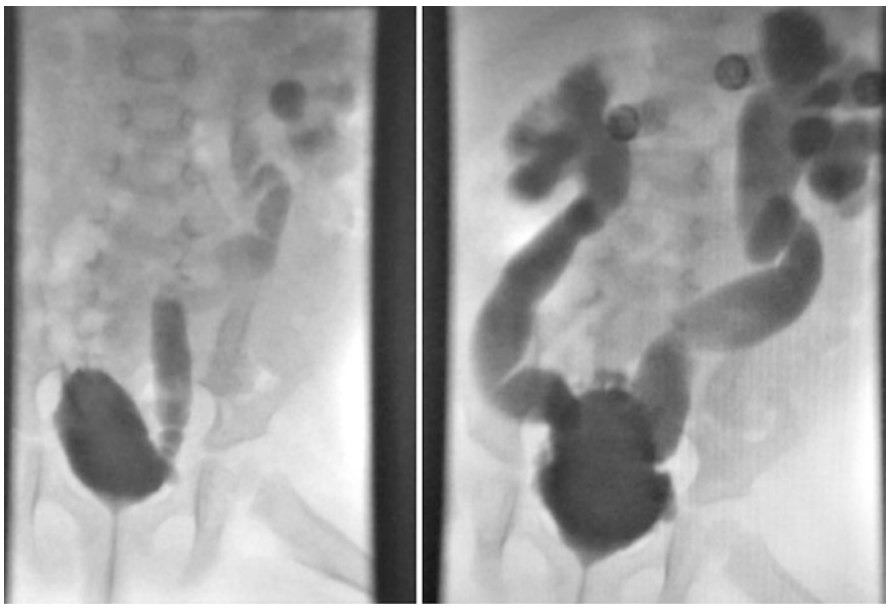

Fig. 15.4 High-grade vesico-uretero-renal reflux

the bladder and upper urinary tract secondary to NLUTD, such as (pseudo-) diverticula, neurogenic bladder conformation, vesico-uretero-renal reflux, hydronephrosis, reflux into the seminal vesicles and prostate. Video-urodynamic follow-up is often indicated for patients with spinal cord injuries and allows early detection of risk factors that precede renal deterioration [33].

15.12.1.2 Bladder Outlet Obstruction

Video-urodynamics are considered the technique of choice for evaluation of women with suspected bladder outlet obstruction [35–37], especially when there is suspected anatomical cause (e.g. after mid-urethral sling surgery). Combining pelvic floor electromyography may also be of great value for differential diagnosis (e.g. dysfunctional voiding).

It is important to remember that video-urodynamics provides a topographic diagnosis of the bladder outlet obstruction. Thus, it provides accurate information for young men with suspected primary bladder neck obstruction ("Marion's disease"), and for patients with suspected urethral stenosis or bladder neck sclerosis after radical prostatectomy.

15.12.1.3 Lower Urinary Tract Dysfunction in Children

Video-urodynamics represent an important diagnostic tool in children with suspected vesico-uretero-renal reflux, especially when there is NLUTD (e.g. meningomyelocele) and other congenital abnormalities (such as posterior urethral valve).

The occurrence of high-grade vesico-uretero-renal reflux (VUR) in patients with neurogenic detrusor overactivity and detrusor-sphincter dyssynergia may underestimate changes in bladder compliance and cystometric capacity during the conventional urodynamic study (Fig. 15.4).

Table 15.3 Summary for video-urodynamics

Summary for video-urodynamics
• Although there is a lack of high-level evidence studies, there is expert consensus on the additional value of video to UDI and video-urodynamics are generally considered to be the gold standard for assessing neuro-urological patients.
• Video-urodynamics can detect vesico-uretero-renal reflux, bladder trabeculation, (pseudo-)diverticula, reflux into the seminal vesicles and prostate and also differentiate between bladder neck vs. rhabdosphincter dyssynergia (detrusor internal sphincter dyssynergia versus detrusor external sphincter dyssynergia).
• There is not standardization for the imaging protocol. Radiation dosage and exposure time represent limitations to be taken into consideration before indicating video-urodynamics. Ionizing radiation should be kept to a minimum according to the as low as reasonably achievable (ALARA) principle.

15.12.1.4 Evaluation of Artificial Urinary Sphincter Function

Video-urodynamics may also help in the evaluation of patients with implanted devices in the lower urinary tract, such as the artificial urinary sphincter (AUS) (Table 15.3). This is true for centers that use contrast medium to fill up the system. Malfunctioning of AUS may be related to mechanical failure of implanted components (reservoir, control pump, cuff), urethral erosion, leak of fluid from the system.

15.12.1.5 Safety

The main risks of UDI are associated with urethral catheterization. If the patient's sensation is preserved, dysuria is quite common in the first days following UDI. Patients with

impaired bladder and urethral sensation are at risk for more severe complications since catheterization problems may not be recognized promptly due to impaired urogenital sensation.

Prophylactic antibiotics reduce the risk of bacteriuria, but not of urinary tract infection after UDI [38]. Thus, antibiotic prophylaxis is not generally recommended, especially when taking into account the alarming prevalence of antibiotic resistance worldwide.

A relevant issue in SCI patients, particularly in those with a lesion at or above T6, is UDI-induced autonomic dysreflexia (AD) [39, 40]; overall incidence is up to 73%. Thus, if available, continuous cardiovascular monitoring during UDI is strongly recommended. In the case of AD during examination, stopping UDI and immediate emptying of the bladder is mandatory to avoid a life-threating situation, and further treatment (e.g., with nifedipine) may become necessary [39].

A history of potential allergies is important, especially considering the allergic potential of latex gloves, catheters, and contrast media.

15.12.2 Ultrasound

This technique involves the simultaneous display of real-time ultrasound images of the LUT along with urodynamics. Ultrasound provides information on the bladder neck position during storage and voiding phases, presence of ureteral dilatation and other morphological abnormalities of the LUT (e.g. pseudodiverticulae, increased bladder wall thickness, presence of intravesical prostatic protrusion in men with benign prostatic enlargement, etc.). Doppler techniques also allow the identification of vesico-ureteral reflux, associated or not with involuntary detrusor contractions.

Ozawa et al. [41] described a totally non-invasive transperineal urodynamic technique using Doppler ultrasonography for videourodynamics. Despite normal urine doesn't have blood cells so urine was thought not to produce Doppler effects, basic studies confirmed that the decrease of pressure at high velocity (Bernoulli effects) caused dissolved gas to form microbubbles, which were detected by Doppler ultrasound. Transperineal Doppler ultrasound was previously correlated with the bladder outlet obstruction index (BOOI) in men with BPE [42], with promising results.

15.12.3 Key-Points: Video-Urodynamics

Video-urodynamics represent an important diagnostic tool for selected patients and are regarded as the gold standard for assessing neuro-urological patients. However, there is an urgent need for standardization of the imaging protocol and ionizing radiation should be kept to a minimum according to the as low as reasonably achievable (ALARA) principle.

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Ambulatory Urodynamics

16

Stefan De Wachter

In the management of patients with SCI, a correct diagnosis and treatment of the associated neurogenic lower urinary tract dysfunction (NLUTD) is necessary to preserve renal function, prevent complications and improve patient's quality of life. Video-urodynamics (VUDS) is the gold standard test for diagnosis of NLUTD. However, the physiological nature of VUDS is often questioned because of the use of radiological contrast (which has a different density than urine) and is instilled at a lower temperature. Furthermore, the bladder is retrogradely filled, often at a rate higher than physiological filling rates. Also, the patient is placed in an artificial environment, which may also affect lower urinary tract dynamics.

Ambulatory urodynamics (AUDS) may theoretically be a more physiological test to evaluate lower urinary tract function as the bladder is filled through normal diuresis, the investigation can be performed in the patient's own environment (e.g. Home or rehab center) and can also be conducted for a longer period of time allowing the patient to perform normal activities. However, the procedure is time-consuming and technically challenging, making it more prone to artefacts.

In non-neurogenic patients AUDS has been shown to be more sensitive to detect detrusor overactivity [1], although it's currently being used when conventional UDS are inconclusive. Only limited and yet conflicting data are available on the use of AUDS in patients with neurogenic LUTD. No agreement was found in parameters relevant to the management of NLUTD between VUDS and AUDS when only one filling cycle was evaluated during AUDS [2]. On the other hand, AUDS was more sensitive to detect detrusor overactivity, an important parameter in the management of NLUTD, if an extended evaluation of nearly 5 h duration was used [3]. At best, based upon the available data, AUDS with extended evaluation periods may be considered if conventional VUDS is inconclusive but one should be aware that extended periods AUDS for 5 h may be time-consuming to perform and analyze the data and prone to artefacts.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_16

Provocative Tests During Urodynamics

17

Stefan De Wachter

Provocative tests during urodynamics including fast filling cystometry with cooled saline ("ice water test") and the bethanechol test are described in this chapter.

17.1 Fast Filling Cystometry with Cooled Saline ("Ice Water Test")

The ice water test (IWT) was first described by Bors and Blinn in 1957 in patients with SCI to differentiate between upper and lower motor neuron lesions. Instilling cold water (4 °C) in the bladder elicits a C-fiber mediated spinal reflex resulting in detrusor contraction [1]. In healthy individuals, the ice water test is positive at toddler's age and becomes suppressed by centrally inhibition [2]. This reflex however may become positive by neurological disorders such as cerebrovascular accident, multiple sclerosis, Parkinson's disease, SCI and spina bifida [2].

The test is performed by rapidly instilling cold water (4 °C) by a syringe or at high filling speed (100 mL/min). The test is positive upon occurrence of a detrusor contraction. Positive ice water tests have been described in 97% and 91% of patients with respectively with complete or incomplete upper motor neuron [3], and in 62.5% of patients with cerebrovascular accidents that showed detrusor overactivity [4]. The IWT is negative in patients with lower motor neuron lesions [3, 5]. Furthermore, the IWT can help to detect masked neurological conditions [5]. Repeating the IWT has been shown to increase its positivity [6]. Care should be taken in patients with SCI above T6 due to the occurrence of autonomic dysreflexia upon ice water instillation.

17.2 Bethanechol Test

The bethanechol test is a method developed to detect lesions in the most peripheral site [7]. It's been described to aid in the diagnosis of lower motor neuron lesion or bladder denervation/detrusor areflexia, but there is a lot of controversy around the clinical utility of the test. This has made current use of the test rather limited. A small amount of bethanechol (2.5–5 mg), a cholinergic agent, is injected subcutaneously. That small dose generally doesn't increase bladder pressure in normal subjects. However, when the bladder is denervated, an upregulation of cholinergic receptors may lead to increases in detrusor pressure. Sensitivity and specificity to detect neurologic detrusor areflexia have been described up to 90% and 96%, respectively [8], whereas false negative rates have been noted up to 24% and false positive rates up to 50% [9]. Therefore if the test is used, the results should be interpreted cautiously, also bearing in mind that strong general reactions (tachycardia, excessive sweating, diarrhea) can occur upon the strong parasympathetic input.

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Urodynamic Findings of Neurogenic Bladder

18

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Abstract

Urodynamics (UDS) is the term used to describe testing and measurements of the function of the lower urinary tract and is the only method that can objectively assess dysfunction during bladder filling, storage, and emptying. UDS is a crucial component of the urologic evaluation of patients with neurogenic lower urinary tract dysfunction (NLUTD). The Madersbacher classification system describes several NLUTD symptoms on the basis of the contraction state of the bladder and external urethral sphincter during the voiding and filling phases of UDS. The evaluation of a patient with neurogenic bladder dysfunction with UDS/VUDS provides a powerful tool in the identification of the type of lower urinary tract dysfunction which can help to direct further management.

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18.1 Lower Urinary Tract Dysfunction

Urodynamics (UDS) is the term used to describe those studies which assess the function of the bladder and its outlet during the filling/storage and emptying phases of the micturition cycle. UDS is the only method that can objectively assess the dysfunction of the lower urinary tract (LUT). The AUA/SUFU guideline on urodynamic studies in adults states that clinicians should perform a post void residual assessment, complex cystometrogram (CMG), and pressure-flow studies during initial urological evaluation of patients with relevant neurological conditions with or without symptoms and as part of ongoing follow-up when appropriate [1]. The EAU Guidelines state that video urodynamics (VUDS) is the gold standard for invasive UDS in patients with neurogenic lower urinary tract dysfunction (NLUTD) [2].

The International Urodynamic Basic Spinal Cord Injury (SCI) dataset [3] recommended data to be included in the urodynamic evaluation of patients with SCI include:

- Bladder sensation during filling cystometry.
- Detrusor function and compliance during filling cystometry.
- Sphincter(s) function during bladder filling.
- Detrusor/sphincter(s) function during voiding.
- Detrusor leak point pressure in patients with impaired detrusor compliance.
- Cystometric bladder capacity and post-void residual.

The urodynamic findings in patients with neurogenic bladder differ greatly based on underlying pathophysiology. Several classification systems have been proposed for NLUTD. The Madersbacher classification system [4] describes several NLUTD symptoms on the basis of the contraction state of the bladder and external urethral sphincter during the voiding and filling phases of UDS (Fig. 18.1). While the normally functioning LUT is composed of a normoactive detrusor and normoactive urethral sphincter, either of these may become overactive or underactive as a

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_18

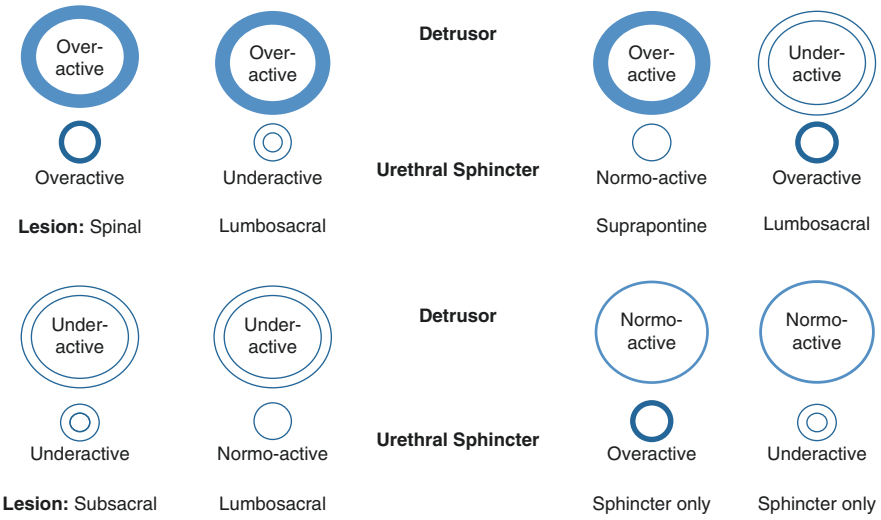

Fig. 18.1 The Madersbacher classification system with typical neurogenic lesions. Adapted from Madersbacher et al. [4]

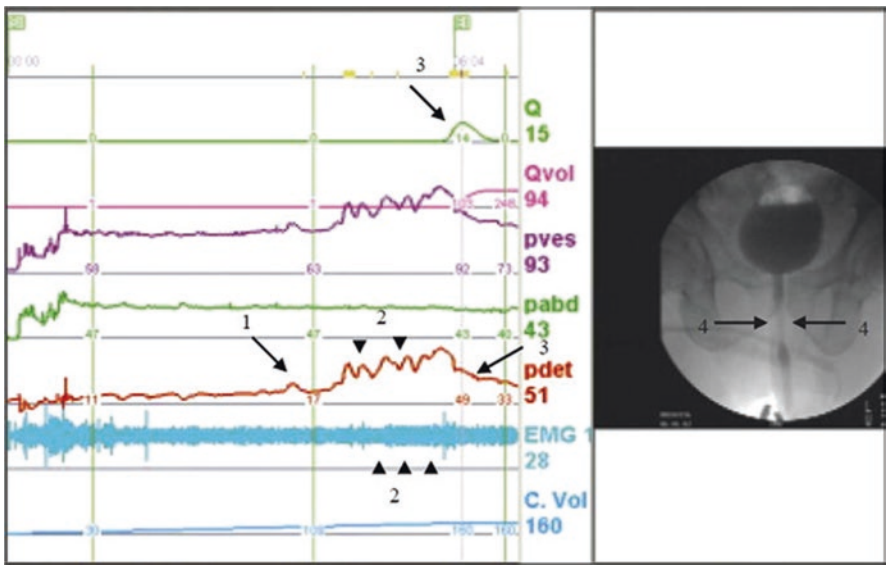

Fig. 18.2 VUDS study revealing detrusor overactivity elicited at a volume of 108 mL (arrow 1). Arrowheads 2 show a setrusor pressure (Pdet) that was high and poorly sustained while the patient had a further increase in sphincter activity during this urge to void. After 2 min of detrusor contraction, the sphincter began to relax and urine started to flow at a Pdet lower than the maximal Pdet (arrows 3). Corresponding fluoroscopic image during voiding showed the bladder neck, a patent prostatic urethra, and a narrow urethral sphincter (arrows 4) [7]

consequence of neural system lesions or dysfunction. The evaluation of a patient with neurogenic bladder dysfunction with UDS provides a powerful tool for the identification of the specific dysfunction and can help to further direct treatment management. In this chapter, we will discuss the various urodynamic findings in patients with NLUTD based on the Madersbacher classification system.

18.1.1 Detrusor Overactivity

Detrusor overactivity (DO) is a urodynamic observation characterized by involuntary detrusor contractions (IDCs) during the filling phase on cystometrogram that may be spontaneous or provoked (Fig. 18.2) [6]. According to the International Continence Society (ICS) terminology, neurogenic DO is when a patient has DO and an associated relevant neurologic condition (e.g. spinal cord injury, multiple sclerosis). Alternatively, DO observed on UDS in the absence of a known neurologic condition is defined as idiopathic DO. IDCs on a urodynamic tracing appear as a rise in total bladder pressure and detrusor pressure but no change in intraabdominal pressure unless abdominal straining occurs. DO can occur in the setting of a normoactive, overactive, or underactive striated urethral sphincter.

Neurologic lesions above the level of the brainstem that affect micturition, with some exceptions, typically result in IDCs with coordinated sphincter function (smooth and striated). These patients usually have preserved sensation and voluntary striated sphincter function but may have incontinence due to the DO [4]. Examples of these conditions include patients who have had a cerebrovascular accident, brain tumor, cerebral palsy, Parkinson's disease, multiple system atrophy, and multiple sclerosis.

Patients with complete lesions of the spinal cord between the levels of T6 and S2 can exhibit IDCs, absent sensation,

smooth sphincter coordination, and striated sphincter dyssynergia. Patients with lesions above the level at T6 may also experience smooth sphincter dyssynergia and autonomic hyperreflexia. Patients with suprasacral spinal cord injuries may have incontinence due to DO. Alternatively, the patient may have outlet obstruction due to smooth (above T6) and striated sphincter dyssynergia resulting in incomplete emptying or complete urinary retention and overflow incontinence.

18.1.2 Sphincter Overactivity: Non-relaxing Urethra and Nonrelaxing Bladder Neck

Sphincter coordination is a necessary component of normal voiding requiring the external (striated) sphincter to relax followed by detrusor contraction. During normal voluntary voiding, the external and internal sphincter should remain relaxed until voiding has been completed [6]. On UDS, this normal relaxation of the sphincter appears as a fall in urethral pressure with relaxation of the external sphincter measured by electromyography (EMG) activity, followed by a rise in detrusor pressure with initiation of bladder contraction [8]. A normal guarding reflex to inhibit an IDC may be observed with EMG activity increasing in the setting of an involuntary contraction, and it is important that the clinician distinguishes between these occurrences in a UDS study.

Within the urethral sphincter complex, smooth sphincter activity may be synergic or dyssynergic and striated sphincter activity may be synergic, dyssynergic, bradykinetic, have impaired voluntary tone, or fixed tone (Table 18.1). Sphincter overactivity can be seen in a variety of neurologic conditions and is demonstrated on urodynamics by increased or maintained EMG activity (Fig. 18.3). An overactive sphincter can result in a high-pressure system due to marked outlet resistance and high amplitude DO or elevated detrusor leak point pressure putting the upper tracts at risk for renal damage.

18.1.3 Detrusor External Sphincter Dyssynergia (DESD)

Detrusor external sphincter dyssynergia (DESD) occurs when there is an involuntary increase in external sphincter activity associated with DO or volitional voiding (Fig. 18.4). Complete spinal cord injury above the sacral spinal cord may result in DESD, leading to a functional obstruction with the

Table 18.1 Most common patterns of voiding dysfunction in patients with various types of neurologic disease or injury

Disorder	Detrusor activity	Compliance	Smooth sphincter	Striated sphincter	Other
Cerebrovascular accident	Ov	N	S, ±VC	S	May have decreased sensation
Brain tumor	Ov	N	S	S	May have decreased sensation
Cerebral palsy	Ov	N	S	S, D, ±VC	
Parkinson disease	Ov, I	N	S	S, Bradykinesia	
Multiple system atrophy	Ov, I	N, decreased	Op	S	Striated sphincter may exhibit denervation
Multiple sclerosis	Ov	N	S	S, D	
Suprasacral spinal cord injury	Ov	N	S	D	
Sacral spinal cord injury	A	N, decreased (may develop)	CNR, Op (may develop)	F	
Autonomic dysreflexia	Ov	N	D	D	
Myelodysplasia	A	N, O	Op, decreased (may develop)	F	
Tabes, pernicious anemia	I, A	N, increased	S	S	Loss of sensation. Detrusor may become decompensated due to overdistention
Disk disease	A	N	CNR	S	Striated sphincter may show evidence of denervation and fixed tone
Radical pelvic surgery	I, A	Decreased, N	Op	F	
Diabetes	I, A, Ov	N, increased	S	S	

Adapted from Wein and Dmochowski [5]
Key:
- Compliance: *N* normal; increased; decreased
- Detrusor activity: *A* areflexia; *I* impaired; *Ov* overactive
- Smooth sphincter: *CNR* competent, nonrelaxing; *D* dyssynergic; *Op* open, incompetent at rest; *S* synergic
- Striated sphincter: *D* dyssynergic; *F* fixed tone; *S* synergic; *±VC* voluntary control may be impaired

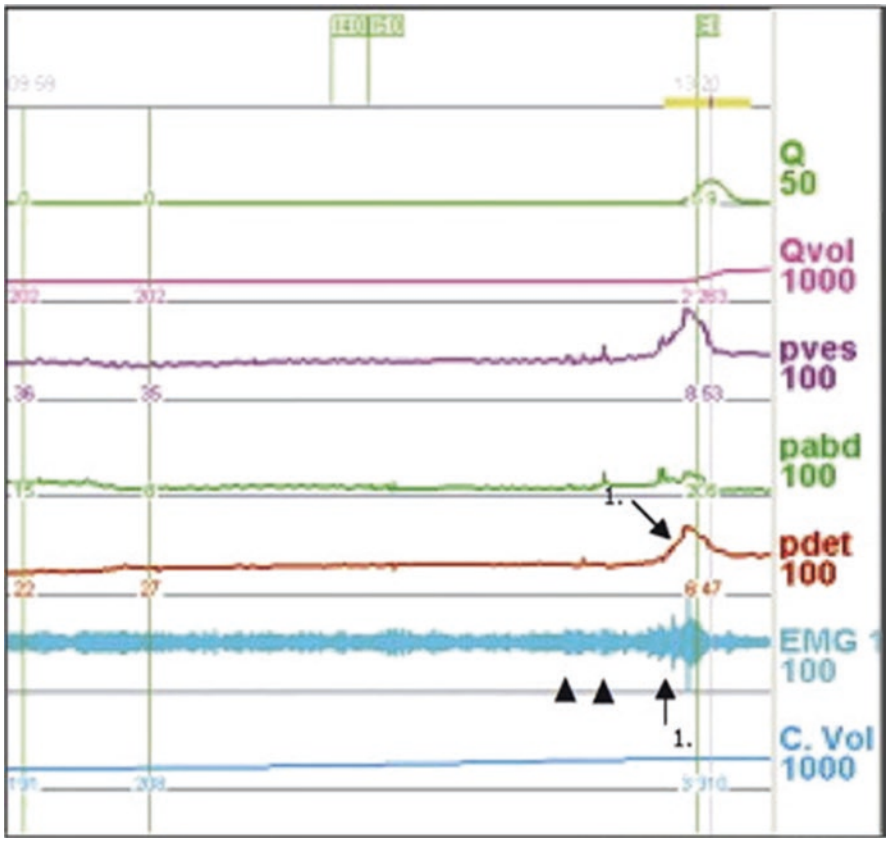

Fig. 18.3 Increased urethral sphincter electromyography (EMG) activity was noted when the bladder was almost full (arrowheads). Sphincter EMG activity increases even further when detrusor contraction begins (arrow 1). Urethral EMG activity subsides during volitional voiding [7]

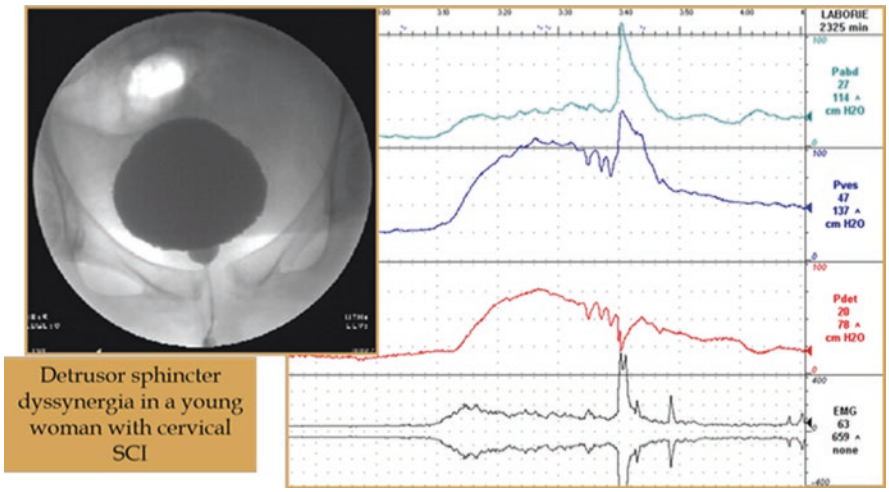

Fig. 18.4 Cystometrogram tracing and corresponding fluoroscopic image of a young woman with cervical spinal cord injury (SCI) showing detrusor sphincter dyssynergia. Image courtesy of LABORIE

detrusor muscle contracting against a relatively closed sphincter [9]. Other common conditions resulting in DESD include multiple sclerosis, spinal dysraphism, and transverse myelitis [10]. DESD can result in high pressures within the bladder leading to long periods of elevated detrusor pressures during filling or voiding which put the upper urinary tract at risk [11–13].

There are three main types of detrusor sphincter dyssynergia (DSD). In type I there is a synchronous increase in the Pdet and sphincteric tone until the peak of detrusor function. Once detrusor function peaks, the sphincteric tone relaxes and unobstructed voiding is allowed to occur. In type II DSD, sporadic contractions of the sphincter occur throughout the detrusor function. Similar to type I, type III DSD also has

increasing sphincter tone throughout detrusor contraction, however with type III, relaxation is never observed thus resulting in obstructed voiding [14].

Classic fluoroscopic findings during video urodynamics for a male patient with DESD would show a narrowing at the membranous urethra with contrast pooling in the prostatic urethra during the voiding phase. Vesicoureteral reflux (VUR) and a "Christmas tree" bladder may also be seen, suggesting long term obstruction [15]. A similar appearance on VUDS may be observed in patients without a neurologic condition, however, these patients are diagnosed as "dysfunctional voiders" as the diagnosis of DESD is reserved for those with a known neurologic lesion above the sacral micturition center.

18.1.4 Detrusor Bladder Neck Dyssynergia (DBND)

Detrusor bladder neck dyssynergia (DBND) is defined as an incomplete opening of the bladder neck during voluntary or involuntary voiding or bladder neck dysfunction from smooth sphincter dyssynergia (Fig. 18.5). This is found mostly in patients with spinal lesions above the level of T6–T8 in the setting of autonomic hyperreflexia and may also be referred to as smooth sphincter dyssynergia or proximal sphincter dyssynergia. The cystometrogram tracing for a patient with DBND will appear similar to that of a patient with DESD with increased sphincter EMG activity in the setting of attempted voiding, however the fluoroscopic images will show obstruction at the level of the bladder neck [16]. Schurch et al. [16] were able to demonstrate DBND to be distinctly different from DSD by showing that while DSD disappeared after bilateral pudendal nerve block, DBND remained unchanged.

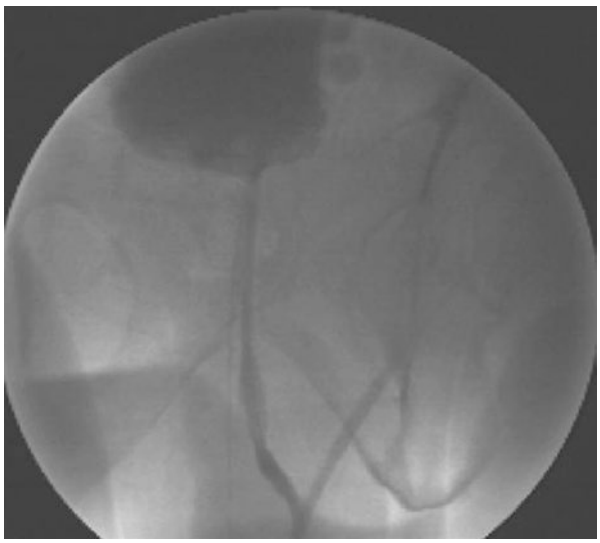

Fig. 18.5 Fluoroscopic image of a non-relaxing bladder neck in a young male with primary bladder neck obstruction

18.1.5 Detrusor Underactivity, Acontractility and Areflexia

Detrusor underactivity, acontractility, and areflexia may be seen in neurologic conditions with trauma or disease below the S2 level of the spinal cord or with interruption of the peripheral reflex arc [4]. In a patient with damage to the sacral cord or roots, UDS will typically show detrusor areflexia, a competent but nonrelaxing smooth sphincter and a striated sphincter that retains some fixed tone but is not under voluntary control [9]. Initially, bladder compliance will be normal or high but decreased compliance may develop over time [17–19].

Patients with detrusor underactivity, acontractility and areflexia may attempt to void by straining or Credé maneuver with an increase in intraabdominal pressure. This may or may not be successful depending on the individual's sphincter [9, 18]. The importance of UDS is stressed in this patient population as elevated post void residual, symptoms of hesitancy, straining to void, and slow stream can be present in both bladder outlet obstruction and detrusor underactivity with a diagnosis easily deciphered through the use of UDS.

18.1.6 Sphincter Underactivity and Acontractility

A normal striated sphincter mechanism shows activity during the filling cycle as manifested by increasing recruitment as the bladder volume increases [14]. Urethral sphincter underactivity or acontractility leads to incontinence at low pressures and with low volumes of leakage (Fig. 18.6). The urethral sphincter may be underactive or acontractile in several NLUTD scenarios and may manifest clinically as urinary incontinence in the setting of a normoactive or hyperactive detrusor muscle. EMG may show striated sphincter denervation appearing as a decreased interference pattern, fibrillation, positive sharp waves, and polyphasic potentials [20]. Patients with sphincter underactivity and acontractility, as seen commonly in patients with cauda equine syndrome, may have an open bladder neck on CMG and fluoroscopy and therefore use of video in these situations is critical for accurate diagnosis.

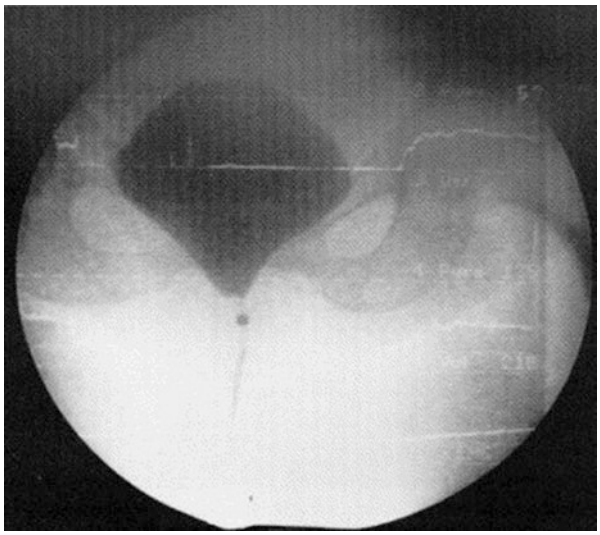

Fig. 18.6 Fluoroscopic image of a female patient with urethral hypermobility, a small cystocele, and a low abdominal leak point pressure consistent with intrinsic sphincter deficiency or sphincter underactivity [21]

Urinary leakage due to sphincteric and/or bladder neck dysfunction can be measured by abdominal leak point pressure (ALPP), an indirect measurement of the ability of the urethra to resist changes in abdominal pressure as an expulsive force [21]. ALPP can be used to determine the degree of sphincter incompetence and presence of stress urinary incontinence [8]. In a patient with a normal urethral sphincter, there is no physiologic abdominal pressure that should cause incontinence and therefore there is no "normal" ALPP.

18.1.7 Hyposensitivity or Hypersensitivity

Sensation during urodynamics is truly subjective and requires an alert and attentive clinician and patient during filling cystometrogram for accurate reporting. Bladder sensation is reported in relation to the bladder volume at the moment in which the patient reports that sensation [22]. Normal bladder sensation can be defined by three points during filling cystometry: first sensation of bladder filling, first desire to void, and strong desire to void [23].

Patients with NLUTD can have alteration in their bladder sensation. Reduced or absent bladder sensation may be present in which the patient has diminished or no sensation of filling at all. Alternatively, bladder sensation may be nonspecific in which the patient is aware of bladder filling because of other sensations such as abdominal fullness, vegetative symptoms, or spasticity. Others may perceive filling as suprapubic discomfort, tingling, and/or burning. Patients with autonomic dysreflexia may have paroxysmal hypertension due to bladder distention and may only have associated symptoms as an indication of bladder filling.

Urgency is defined as a sudden compelling need to void that is difficult to defer. Urgency should be recorded on the urodynamic tracing and is one of the defining characteristics of overactive bladder [6]. Yamaguchi et al. [24] suggested that urgency is triggered suddenly when stimulation to bladder afferent nerves exceeds a certain threshold. In a study by Griffiths [25], functional MRI was used to examine individual brain regions important in bladder sensation and control. Normal bladder filling sensation was found to be mapped mainly in the insula. These areas shifted anteriorly as sensation became stronger and more unpleasant and the patterns themselves became abnormal in patients with poor bladder control. Patients with NLUTD can have altered bladder sensation leading to hypersensitivity and urgency, manifesting as reported urgency or a greater desire to void at lower volumes on CMG.

18.1.8 Reduced Detrusor Compliance

Bladder compliance is defined by the ratio of the increase in intravesical pressure over the increase in bladder volume ($\Delta V/\Delta P$) corresponding to the capacity of the detrusor to allow bladder filling at a low pressure. Several neurologic conditions can lead to decreased compliance including multiple sclerosis, Parkinson's disease, dementia, and spina bifida [14]. Decreased compliance resulting in elevated storage pressure, observed as an elevated detrusor leak point pressure on UDS, can lead to upper tract deterioration and should be treated to prevent renal damage.

Bladder compliance measurements during UDS assume that the bladder approximates a spherical shape during filling and that the pressure equalizes throughout the bladder. The use of fluoroscopy during UDS is exceptionally important in the NLUTD population in order to assess for abnormal bladder shape or detrusor pressure shifting to a bladder diverticulum or vesicoureteral reflux (Fig. 18.7).

18.1.9 Abnormal Bladder and Urethral Shape

See Chap. 20.

18.2 Upper Urinary Tract Dysfunction

Upper tract risk factors are related to intravesical pressure and the detrusor leak point pressure. The therapeutic goal is always low-pressure storage with periodic emptying [5].

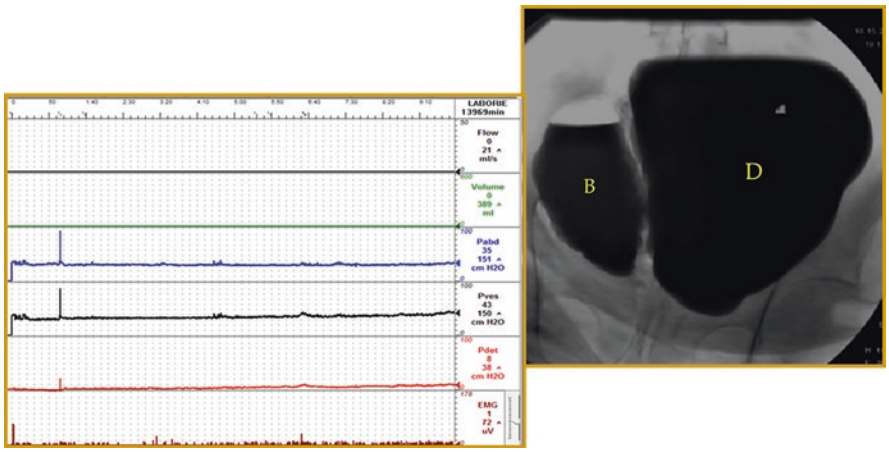

Fig. 18.7 Cystometrogram tracing and corresponding fluoroscopic image of a patient with decreased compliance. Note the rise in intravesical pressure. This patient has a large bladder diverticulum which can be seen on the fluoroscopic image. Image courtesy of LABORIE. *B* bladder, *D* diverticulum

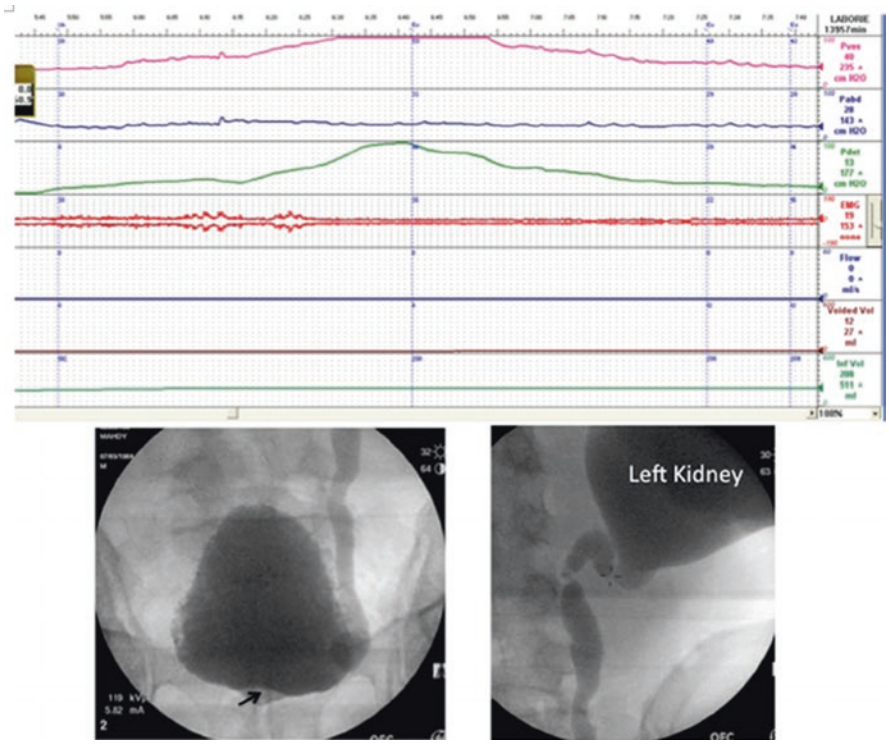

Fig. 18.8 Videourodynamics study of a male presenting with nocturnal enuresis. The pressure-flow study (top) shows bladder outlet obstruction. Voiding cystourethrogram (bottom) shows grade IV left vesicoureteral reflux [27]

18.2.1 Vesicoureteral Reflux

Simultaneous fluoroscopy use during UDS for at-risk neurogenic bladder patients is critical to assess for vesicoureteral reflux (VUR). In cases of VUR, the bladder storage pressure or compliance may report an acceptably safe number, however this is secondary to a "pop off valve" phenomenon in which bladder pressure is decreased by reflux to the upper tracts [26]. When VUR is seen on VUDS, the volume and pressure at which VUR is first identified should be noted. The clinician should also make note of the grade of VUR observed (Fig. 18.8). Appropriate treatment recommendations for bladder emptying and maintaining low intravesical pressures can then be made based on these results. The treatment goal in this situation is to maintain bladder pressures low enough to limit or prevent VUR in order to mitigate progressive renal deterioration.

18.2.2 Hydronephrosis and Ureteral Dilation

Many patients with NLUTD have the potential to develop hydronephrosis through VUR or decreased bladder compliance. As previously discussed, the use of fluoroscopy during

VUDS can identify and grade the degree of VUR and upper tract dilation. In addition to VUR, other factors such as detrusor histopathology may also contribute to elevated storage pressures and upper tract dilation and deterioration. Ozkan et al. [28] performed a study using full-thickness bladder biopsies in a group of patients with neurogenic detrusor overactivity undergoing augmentation cystoplasty. They found that the degree and severity of detrusor fibrosis was a significant risk factor for upper tract dilation and deterioration as was a detrusor leak point pressure of greater than 75 cm H2O. In contrast, disease duration and preoperative catheterization were not found to be associated with upper tract deterioration.

18.3 Conclusions

In summary, management of the urinary tract in patients with neurologic disease or defects should be based on urodynamic principles and findings rather than inferences from the clinical and neurologic history and evaluation. Clinicians must avoid making neurologic conclusions based solely on urodynamic findings and evaluate the complete clinical picture in conjunction with UDS findings when recommending treatment plans for these patients.

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Uro-neurophysiological Evaluation of the Neurogenic Bladder

19

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Abstract

Neurophysiological tests are useful in diagnosis of neurogenic bladder. Electromyography (EMG) of the Pelvic Floor and Sphincter Muscles is a useful neurophysiological test in diagnosing lower motor neuron lesions in the sacral segments, it is useful in demonstrating increased external urethral sphincter EMG activity concomitant with detrusor contraction in patients with detrusor sphincter dyssynergia in some patients with Parkinson's and multiple system atrophy. Nerve conduction studies of pudendal nerve are performed to studies pelvic floor function. The most commonly sacral reflexes tested during neurophysiologic testing of the pelvic floor are the bulbocavernosus reflex and the anal reflex, it tests the integrity of the spinal cord–mediated reflex arc involving Sacral nerves 2–4 and may be absent in the presence of sacral cord or peripheral nerve abnormalities. Sympathetic skin response (SSR) is directly evaluating the pelvic sympathetic innervation include assessment of the urethro-anal and bladder-anal reflexes. It is a useful test in the evaluation of neuropathy involving non-myelinated nerve fibers.

19.1 EMG (in a Neurophysiological Setting) of Pelvic Floor Muscles, Urethral Sphincter and/or Anal Sphincter

Electromyography (EMG) is a term that refers to methods of studying muscle response or electrical activity in response to a nerve's stimulation of the muscle or near the muscle. An electrode detects bioelectric potentials generated by the depolarization of the skeletal striated muscle then filtered and amplified. They are displayed on an oscilloscope for visual analysis. An audio-amplifier is used so they can be monitored acoustically. Modern equipment is computer based which allows for the conversion of the signal into digital data that can be easily stored, processed, and analyzed. In general, external anal sphincter EMG will be the same as the external urethral sphincter EMG except in some neurological disease. The two most common electrodes used in EMG are surface electrodes which are self-adhesive skin patch electrodes that are applied to the skin of anal sphincter and needle electrodes. Other electrodes are anal plug and urethral catheter–mounted electrodes [1, 2]. Both surface and needle electrodes have advantage and disadvantage, the advantage of surface electrode is easy to apply, more comfortable, and convenient for the patient. The disadvantage that it has inferior signal compared to the needle electrode so it must be implemented precisely. On the other hand, the needle electrode is painful for the patient, dislodge easily and better for obtaining a signal from the source.

There are two types of EMG studies used for evaluation of pelvic floor disorders, kinesiological EMG (kEMG) and motor-unit EMG [3].

19.1.1 Technique of Needle of EMG

The patient is placed in dorsal lithotomy or lateral decubitus positions that allow access to the pelvic floor musculature. A grounding surface electrode is applied, and usually, local anesthetics are not used before insertion of the needle electrodes. After wiping the skin overlying the proper muscle with alcohol, the concentric needle electrode is embedded until the insertional movement of the muscle is noted, affirming that the terminal is inside the muscle. Concentric needle EMG of the subcutaneous external anal sphincter (EAS) muscle is more useful for diagnosing neurogenic LUT dysfunction because of it is easy to access and has enough

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_19

muscle bulk for accurate EMG analysis [4]. Several sites within the muscle should be sampled which is difficult in small muscle. External urethral sphincter (EUS) examination is hampered by technical difficulties and small muscle bulk, which makes the validity of quantitative analysis questionable [5, 6]. Levator ani and bulbocavernosus muscles also can be examined with EMG.

Both the superficial and deep parts of the external anal sphincter (EAS) are accessible for EMG evaluation, in most of the cases only EMG of the subcutaneous EAS is needed. To study the subcutaneous portion of EAS, the needle electrode is inserted into the subcutaneous EAS muscle, about 1 cm from the anal orifice, to a depth of 3–6 mm under the non-keratinized epithelium. To study the deep portion of EAS, the needle inserted 1–3 cm deep at the anal orifice at an angle of 30° to the anal canal axis [7, 8].Commonly the subcutaneous, as well as deep part of the EAS, are examined in no less than four quadrants, approximately divided into the upper and lower and left and right portions of the sphincter. Preferably, at least 20 MUAPs ought to be examined amid the assessment.

The external urethral sphincter (EUS) can be examined by the periurethral approach; the needle is inserted around 5 mm anterior to the external urethral meatus at 12:00 position to a depth of 1–2 cm [4]. EUS also can be examined by the transvaginal approach, and the posterior vaginal wall is retracted with a speculum, and the needle is inserted around 2 cm proximal to the external urethral meatus, off the midline, and directed laterally into the urethral sphincter [5].

Needle insertion can examine the bulbocavernosus muscle through the skin lateral to the labia majora or mucosa medial to the labia minor [9].

The iliococcygeus and pubococcygeus portions of the levator ani muscle complex are examined using a transvaginal approach. Levator ani complex muscle are identified by inserting two fingers into the vagina and asking the patient to contract. Muscle isolated by one hand and the electrode is inserted using the opposite hand in at least two sites on the muscle then repeated on the opposite side. The puborectalis muscle can be examined using a perineal approach with a needle insertion approximately 1 cm posterior to the anus in the midline for a depth of 3–5 cm.

19.1.2 Kinesiological EMG (kEMG)

kEMG is usually used with urodynamics and anal manometry to evaluate sphincter relaxation during voiding and defecation. It is useful in demonstrating increased external urethral sphincter EMG activity concomitant with detrusor contraction in patients with neurologic disease (detrusor sphincter dyssynergia in some patients with Parkinson's and MSA) [10] and in patients without neurologic disease (dysfunctional voider) [11]. Also used for biofeedback during the treatment of fecal and urinary incontinence. It is to assess if there is an activity or no activity of muscle, usually the urethral or anal sphincter.

19.1.3 Motor-Unit EMG

The EMG investigation consists of the analysis of electrical activity at rest, at slight voluntary contraction and at strong contraction.

Motor-unit EMG is a diagnostic tool used to assess the neuromuscular function of muscle. It can differentiate normal muscle from myopathic or denervated muscle. A common technique used for motor-unit EMG is concentric needle EMG (CnEMG). Single-fiber EMG (SfEMG) is an established technique for motor-unit EMG but not recommended for use in clinical practice [12].

"Concentric Needle Electromyography of the Pelvic Floor and Sphincter Muscles is useful in diagnosing lower motor neuron lesions in the sacral segments (e.g., cauda equina or conus medullaris lesions, multiple system atrophy [MSA]) by demonstrating denervation activity, reinnervation changes, and a reduced recruitment pattern" [6]. Isolated the upper motor neurons lesions have a normal EMG evaluation.

A concentric needle electrode is a single use electrode and consists of fine insulated silver, steel, or platinum wire (except the tip not insulated) which run through steel outer cannula. Bioelectrical potentials are measured as voltage differences between the wire which serve as a recording electrode and the cannula which serves as a reference electrode that is then recorded, displayed, and analyzed.

CnEMG settings for evaluation of the pelvic floor muscles are: filter settings, 5–10 kHz; horizontal sweep speed, 10 ms/div; and gain setting, 50–500 μV/div [9].

If the needle has been properly inserted and no insertional activity was detected, this means complete atrophy of the muscle. After that, assessment of spontaneous activity at rest by asking the patient to relax the muscle being tested completely. At rest state, the normal spontaneous activity is normal motor unit action potentials (MUAP) in the urethral sphincter, the levator ani muscles and the anal sphincter, which all tonically contract at rest. In contrast, it should be the complete absence of spontaneous activity in the bulbocavernosus muscle, which does not tonically contract at rest. During voiding and defecation, the pelvic floor muscles normally have complete electrical silence. Abnormal spontaneous activity includes fibrillation potentials, fasciculations, myotonia, complex repetitive discharges positive sharp waves, myokymia, and neuromyotonia.

Then slight voluntary contraction for MUAP analysis. The duration, amplitude, shape, number of phases, and

stability of each MUAP should be assessed. Normal muscles have distinct MUAP characteristics from those of myopathic, denervated and reinnervated muscles. In Myopathic injury, there will be an MUAP with smaller amplitude and shorter duration due to muscle fiber loss.

After MUAP analysis, the patient instructed to perform strong contraction for motor unit recruitment assessment (interference pattern analysis). When complete interference pattern achieved at the maximal effort, the recruitment considered as normal. In neuropathic disorders, there is incomplete interference pattern due to reduced number of motor units, so recruitment after that. In myopathic disorders, there is complete interference pattern due to normal number of motor units, but occurs at much less than maximal effort and the amplitude to the MUAPs is reduced.

The CnEMG can determine acute and chronic nerve lesions. In an acute nerve lesion, recruitment is decreased due to reduced number of motor units but MUAPs have normal morphology because reinnervation has not yet occurred. Between 2 and 30 days after an injury, insertional activity becomes longer, fibrillation potentials, and positive sharp waves become apparent. Three to six months after an injury, MUAPs become larger and more complex because reinnervation has occurred. The pattern of muscles demonstrating denervation, determine the location of a nerve lesion.

"By means of an EMG tracing from the striated sphincters in cases of neurogenic bladder and rectal disturbances, the following can be determined:

(1) If a disturbance of innervation is present or not. (2) If this lesion affects the central or peripheral motor neuron. (3) The extent of the lesion." [13].

19.2 Nerve Conduction Studies of Pudendal Nerve

The clinical significance of nerve conduction studies draws from the fact that nerve injury affects the rate at which a nerve impulse travels. Pudendal nerve terminal motor latency (PNTML) and perineal nerve terminal motor latency (PeNTML) are performed to studies pelvic floor function.

19.2.1 Technique

St. Mark's disposable electrode is the most commonly used to perform PNTML and PeNTML. It can be done rectally [14], vaginally [15] or by place the needles in bulbocavernosus or external anal sphincter muscles [16].

Commonly approached rectally, the stimulating tip is placed at the level of the ischial spine to stimulate the pudendal nerve. A receiving electrode situated at the level of the external anal sphincter detects the elicited compound motor action potential (CMAP). Stimuli of 0.1 ms duration are applied at 1-s intervals as the stimulating tip is positioned over the pudendal nerve. Transvaginal stimulation used the same technique and range [17, 18].

There is not an agreement for latency to define a patient as abnormal [17, 18]. Usually, the values greater than 2 standard deviations from the mean and is a difference with age and sex [14, 19, 20].

The limitation of PNTML are a poor correlation with clinical symptoms and histologic findings, lack of specificity and sensitivity for detecting external anal sphincter muscle weakness, and it is operator-dependent and no clear prognostic value in predicting surgical outcome [14].

19.3 Reflex Latency Measurements of Bulbocavernosus and Anal Reflex Arcs

The most commonly sacral reflexes tested during neurophysiologic testing of the pelvic floor are the bulbocavernosus reflex and the anal reflex. The bulbocavernosus reflex (BCR), which is representative of sacral nerve root levels 2–4 (S2–4), is present in 70% of normal females and 100% of normal males. It tests the integrity of the spinal cord–mediated reflex arc involving S2–S4 and may be absent in the presence of sacral cord or peripheral nerve abnormalities. A normal reflex requires intact efferent and afferent innervation and normal integration of the two in the sacral spinal cord so BCR assesses the afferent and efferent branches of the pudendal nerve. BCR is a reflex contraction of the striated muscle of the pelvic floor that occurs in response to various stimuli in the perineum or genitalia. Reflex is traditionally elicited by placing a finger in the rectum and then squeezing the glans penis, clitoris or by applying traction to an indwelling Foley catheter to pull the balloon against bladder neck. If the BCR is intact, tightening of the anal sphincter should be felt and/or visualized.

BCR is tested by applying a stimulus to the dorsal clitoral nerve either mechanical, electrical or magnetic and measuring the latency of the reflex response with recording electrodes within bulbocavernosus muscle or anal sphincter [9]. The stimulus is approximately three-times the patient's sensory threshold. The bulbocavernosus reflex has two components. The first element is thought to be an oligosynaptic response and has mean latencies of approximately 33 ms but typically a latency is considered abnormal if it is greater than 45 ms [21]. The second component is thought to represent a polysynaptic suprasacral response and has a latency of approximately 70 ms [22]. In the anal reflex, the stimulus is applied peri-anally, and its average latencies are longer than those of the bulbocavernosus reflex because afferent limb of the reflex arc has thinner myelinated nerve fibers [23, 24].

Absent or prolonged latency in either the bulbocavernosus or the anal reflex may represent any lesion along the reflex arc between the pudendal nerve to the conus medullaris.

Urethro-anal reflex is performed by stimulation the urethra via an electrode mounted on a Foley catheter, and bladder-anal reflex is performed by stimulation the bladder by moving this ring electrode into an empty bladder. Latencies between 50 and 65 ms has been reported normal latencies for these reflexes [22, 24]. Normal bulbocavernosus reflex latency associated with absent or prolonged urethro-anal or bladder-anal reflex latency implies a pelvic plexus lesion or autonomic neuropathy.

19.4 Evoked Responses From Clitoris or Glans Penis: SEP, MEP

19.4.1 Pudendal Somatosensory Evoked Potentials (SEPs)

This test is used to evaluate the integrity of the sensory pathways from the periphery to the parietal cortex. By electrical or mechanical stimulation of the dorsal penile or clitoral nerves Pudendal SEPs can be elicited [25, 26]. Two to four times stronger electrical stimulation than the sensory threshold, is usually applied.

In multiple sclerosis and diabetic cystopathy, pudendal SEPs have suggested being less sensitive than tibial SEPs [27, 28]. Pudendal SEP was claimed to be of no greater value than the neurologic examination in urogenital dysfunction [25]. "Pudendal SEP might be theoretically more relevant than tibial SEP in patients with known neurologic disease in whom the reason for LUT dysfunction is sought." [29].

19.4.2 Sacral Central Motor Conduction Studies: Motor Evoked Potentials (MEPs)

This technique is used to evaluate to motor pathways innervating the pelvic floor and sphincter muscles. MEPs may be useful to assess spinal cord lesions of vascular or metabolic origin which could not be diagnosed on clinical or radiological examination.

Electrical or magnetic stimulation can be used to stimulate the brain. Cerebral electrical stimulation is used only during intraoperative monitoring in the anesthetized patient because it is so painful [30] the coil is usually applied to the vertex during magnetic transcranial stimulation [31]. A coil with a figure eight configuration might be more effective in healthy women than circular coil, detection of sphincter and pelvic floor muscles activation by needle electrodes is recommended, [32] latencies are used in evaluating the response (mean latencies are 20–30 ms, but slight voluntary contraction of the sphincter and pelvic floor muscles shortens the mean latencies to 17–27 ms) [30]. Central conduction time is obtained for the pelvic floor, and sphincter muscles by subtracting the latency of the MEPs achieved by stimulation over the scalp and at the L1 (16 ms without, and 13 ms with, facilitation) [30].

19.5 Sympathetic Skin Response

Sympathetic skin response (SSR) is directly evaluating the pelvic sympathetic innervation include assessment of the urethro-anal and bladder-anal reflexes. It is a useful test in the evaluation of neuropathy involving non-myelinated nerve fibers [33]. SSR represents a potential generated in skin sweat glands (palms, soles and external genitalia); it originates by activation of the reflex arch with different kinds of stimuli. The absence of sweat production is considered abnormal and sweat production is quantified by measuring changes in electrical resistance on the skin [9]. The reflex consists of myelinated sensory fibers, a complex central integrative mechanism and a sympathetic efferent limb with postganglionic nonmyelinated C-fibers. The potential of rapid habituation after repeated stimuli is formed by biphasic or triphasic slow wave activity with relatively stable latency and variable amplitude [34].

Diabetic cystopathy was associated with autonomic neuropathy as detected by SSR [35]. A correlation has been shown between the absence of the SSR response in the foot and bladder neck dyssynergia following spinal cord injury [36].

19.6 Others

19.6.1 Proximal Sacral Motor Conduction Studies

The aim of this test to evaluate the conduction in the lower sacral motor neurons distal to the cauda equina.

It can be delivered at different levels (e.g., L1-S3) and both electrical and magnetic stimulation can be used [31]. Needle detection is necessary due to nonselective stimulation [31]. Recording from the EAS muscles is most common. Transcutaneous electrical stimulation of the S3 motor root has also been described, and by stimulating an individual root, its motor fiber function can be assessed before introducing therapeutic electrical stimulation (particularly implants) [37].

19.6.2 Dorsal Penile Nerve Sensory Studies

This test is not often used. A pair of stimulating electrodes is placed across the glans and a pair of recording electrodes across the base of the penis.

"Theoretically, a normal amplitude sensory nerve action potential of the dorsal penile nerves in an insensitive penis distinguishes a sensory lesion proximal to the dorsal spinal ganglion (e.g., cauda equina, central pathways) from a lesion distal to the ganglion (e.g., sacral plexus, pudendal nerves)" [38].

19.6.3 Peripheral Sacral Sensory Conduction Studies

It has been used intraoperatively to decrease the incidence of postoperative voiding dysfunction through preserving roots important for perineal sensation in spastic children undergoing dorsal rhizotomy [39].

19.6.4 Bladder Smooth Muscle EMG

The aim of this method to evaluate urinary bladder smooth muscle and sacral parasympathetic nerve function. In theory, detrusor EMG would be the most definitive test of neurogenic bladder involvement.

19.6.5 Assessment of LUT Sensation

It has been used in painful bladder syndrome [40]. Recording of perineal surface EMG and palmar SSR during cytometry might be useful in the neurogenic bladder with impaired bladder sensation [41].

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Imaging Techniques in the Evaluation of the Neurogenic Lower Urinary Tract Dysfunction (NLUTD)

20

Jerzy B. Gajewski and Ashley R. Cox

According to ICI 2017 imaging of the upper urinary tract upper urinary tract (UUT) is indicated in cases of NLUTD and urinary incontinence with high risk of renal damage (due to high storage and/or voiding detrusor pressure, e.g., myelodysplasia, spinal cord injury) [1]. There is however no general consensus how frequently this evaluation has been indicated and what test included. European Association of Urology guidelines (EAU) [2] and National Institute for Health and Care Excellence (NICE) guidelines [3] has similar although slightly different recommendations. Currently, the Canadian Urological Association (CUA) and the American Urological Association (AUA) lack guidelines for management of neurogenic bladder. This chapter describes imaging techniques in the evaluation of the patients with NLUTD.

20.1 Ultrasound (US) Examination for Both Upper and Lower Urinary Tract

Ultrasound (US) is considered an inexpensive, versatile and patient friendly method of assessing the genitourinary tract. Disease processes are surveyed in real time without exposure to ionizing radiation. US images result from the interaction of sound waves with tissues and organs. An ultrasound probe, or transducer, is placed in contact with the body and acts as both a sender and receiver of the soundwave. Electrical energy is converted to a mechanical soundwave via a piezoelectric effect of expanding and contracting crystals within the transducer. This mechanical energy then travels through a coupling medium to the skin. Soundwaves traverse the tissues and are propagated back to the transducer based on properties of that tissue (e.g., density, impedance). Once the transducer receives this mechanical energy, it is converted back to electrical energy to create an image [4]. The quality of the image is dependent on several factors, including the resolution and depth of penetration of the soundwave. Structures close to the skin surface can be imaged with high-frequency transducers and result in excellent resolution (e.g., pediatric kidney, testis). Deeper structures require lower frequency transducers (longer wavelength) and result in poorer resolution. Various modes of US exist, with gray-scale B-mode being the most commonly employed. This produces real time, two-dimensional images in shades of gray.

Doppler US is used to characterize motion such as blood flow or flow of urine. It is dependent on the principle of frequency shift when sound waves strike a moving object. When colour Doppler US is used, blue indicates motion away from the transducer while red displays motions towards the transducer. Brighter colour indicates more rapid motion. Power Doppler US may be used as a more sensitive mode for detecting blood flow. In urology, these tests are applicable to identifying devascularized structures (e.g., testicular torsion) or urine flow (e.g., ureteric jets in the bladder). Three dimensional US is available but thus far there is limited application in urology.

Since the 1980s, ultrasound has been recommended for neurogenic bladder patients to detect abnormalities such as hydronephrosis, renal parenchymal disease, renal and bladder calculi and to measure bladder volume and residual urine [5]. More modern use of US incorporates methods to assess bladder wall thickness and morphology in an attempt to predict upper tract damage without the need for invasive urodynamic testing.

20.1.1 Upper Urinary Tract Evaluation

In 2008 Abrams et al. [6] conducted a literature review and review of expert practices in the management of spinal cord injury (SCI) patients. They concluded that renal/bladder US should be done at baseline and at 3–6 month following the injury, followed by annual renal/bladder US and US assessment of post void residual volumes (PVRs). In a 2012

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_20

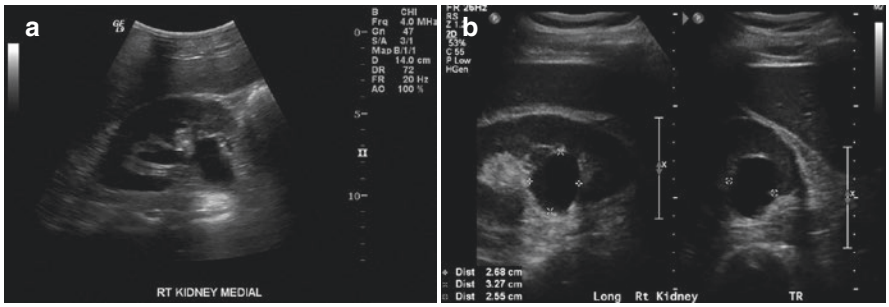

Fig. 20.1 Hydronephrosis (**a**) and renal cyst (**b**) on US

systematic review by Cameron et al. [7], 11 of 12 articles included in the review recommended US as a useful, non-invasive and cost-effective screening method for SCI patients for detecting upper tract abnormalities, including stones. A survey study of 269 American members of the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) found that 80% (n = 128) of respondents reported favouring an annual renal ultrasound for routine surveillance of the upper tracts for neurogenic bladder patients [8].

Despite a lack of evidence to support a specific surveillance strategy, upper tract evaluation using renal US is recommended on a routine basis due to ongoing potential for deterioration of the upper tracts in patients with neurogenic LUTD [9]. The current EAU guidelines for follow-up of neurogenic LUTD suggests assessment of the upper urinary tract, bladder morphology and PVR by US every 6 months, with more stable patients being monitored every 1–2 years [2]. The National Institute for Health and Care Excellence (NICE) 2012 recommendation consists of lifelong US surveillance of the kidneys every 1–2 years for those who are considered high risk of developing renal impairment. This includes those with SCI, myelodysplasia or adverse urodynamic parameters such as decreased bladder compliance, detrusor sphincter dyssynergia (DSD) and vesicoureteric reflux (VUR) [3]. NICE guidelines do not recommend the use of plain abdominal radiography for routine surveillance in people with neurogenic lower urinary tract dysfunction.

20.1.1.1 Hydronephrosis

Spinal Cord Injury

Hydronephrosis in patients with neurogenic LUTD may be a result vesicoureteric reflux or obstruction related to a poorly compliant, thick walled bladder or other cause such as stones. The rate of hydronephrosis was found to be 5.5% over a 6-year study in 1005 patients with SCI. Renal atrophy was detected in 1.2% [10]. Other studies report rates as high as 16% in SCI [11]. Ultrasonography showing dilatation of the upper urinary tract in SCI patients has been shown to increase the risk of both moderate renal deterioration (HR 2.20) and severe renal deterioration (HR 5.68) [12]. In comparison to SCI who are able to void spontaneously, the presence of an indwelling catheter (urethral or suprapubic) increases the risk of renal deterioration in patients with SCI (38.3% vs. 81.5%, $p < 0.001$) [13].

Renal US has a sensitivity and specificity of 96% and 90%, respectively, for the detection of hydronephrosis [14]. There is a false positive rate of detecting hydronephrosis of 10%, which is considered acceptable for a screening test (Fig. 20.1). The detection of hydronephrosis is also less likely to be missed if US is performed with a full bladder, however the false positive rate will be increased [15]. Renal US is recommended for routine surveillance of SCI patients even if asymptomatic. Vaidynanathan et al. compared the results of renal US in SCI who had symptoms pertaining the urinary tract versus those who were asymptomatic. They found that those who were symptomatic at the time of US were more likely to have an abnormality detected that warranted intervention. Ninety-five percent of symptomatic patients required an intervention based on US findings. US is important in the work-up of symptomatic SCI patients in addition to its use as a screening tool for asymptomatic renal complications [16].

The use of renal resistive index (RI) has been assessed in attempt to identify SCI patients with obstructive uropathy. They hypothesized that a RI of 0.7 could be used as a cut off value to identify obstructive uropathy. Ultrasound examination using Doppler to calculate renal vascular RI was used and compared to radioisotopic renography to assess renal function and obstruction. The average RI was 0.58 ± 0.07 in the control group and 0.65 ± 0.8 in the uropathy group ($p < 0.001$). The authors concluded that RI does increase in SCI patients with obstruction but that the cut off of 0.7 could not be used as a marker of obstruction [17].

Myelodysplasia

In addition to SCI patients, those with myelodysplasia and neurogenic LUTD also require ongoing surveillance of their upper tracts with renal US. Children with hydronephrosis on US at the time of initial urology consult have poorer long-term outcomes and a higher rate of renal deterioration compared to patients without hydronephrosis [18]. In a 1996 study, 15% of SB patients developed upper urinary tract

deterioration while 7.5% developed renal failure over a 2–14 year follow-up period [19]. Ma et al. reported unilateral or bilateral hydronephrosis in 38% of 120 spina bifida patients (median age 12.3 years, range 1.5–38). Multivariate analysis revealed that poor compliance, VUR and urinary tract infection (UTI) were risk factors for the presence of hydronephrosis. UTI was the most significant predictor of hydronephrosis (OR 29.6) in this cohort [20]. For these reasons, it is clear that upper tract surveillance is necessary. In this patient population, US may be lacking in ability to detect scarring compared to Tc-99m-dimercaptosuccinic acid (Tc-99m-DMSA) scintigraphy. Renal scarring is thought to increase the risk of long-term renal failure and hypertension in patients with spinal dysraphism. Renal scintigraphy detected scars in 45.9% renal units compared to only 10.3% detected by US ($p < 0.001$). In addition, the scarring detected on renal scan was associated with hypertension ($p = 0.049$), while scarring on US was not ($p = 0.1$) [21].

Multiple Sclerosis (MS)

Upper tract deterioration occurs less frequently in patients with MS. However, some patients will experience renal deterioration. Lemack et al. found 16.7% of MS patients referred for urological assessment were found to have abnormal US findings. Mild unilateral focal caliectasis was the most common. Other abnormalities included: bilateral focal caliectasis, unilateral scarring, unilateral hydronephrosis, and renal calculi. Predictors of abnormal upper tracts were not identified. Most abnormalities of the upper tract were thought to be of little clinical significance [22].

20.1.1.2 Stones

The estimated incidence of stones in patients with neurogenic LUTD is 5–11% [23]. Within 10 years of a SCI, 7% of patients will develop kidney stones [24]. Ultrasound has an estimated sensitivity of 88.7% and specificity of 68.3% for detecting kidney stones when compared to CT scan as a reference in a cohort of patients without neurogenic LUTD [25]. In the neurogenic patients population, the sensitivity and specificity are presumably lower due to factors such as body habitus, skeletal abnormalities and abnormalities in renal morphology. However, US remains the preferred modality for surveillance for stones due to availability, cost and the lack of radiation exposure (Fig. 20.2). It is preferable to KUB due to its ability to detect other genitourinary abnormalities at the same time [26].

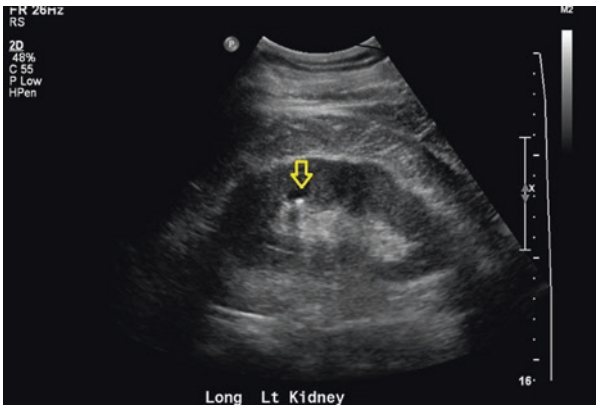

Fig. 20.2 Stone in the L kidney on US

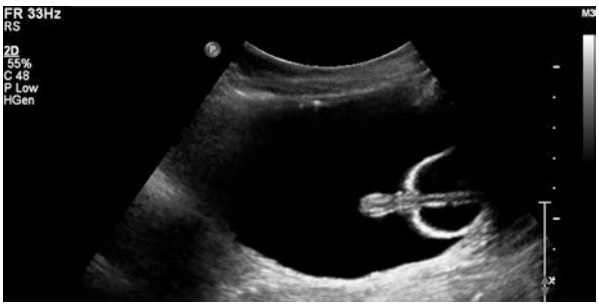

Fig. 20.3 Foley catheter in the bladder

20.1.2 Lower Urinary Tract Evaluation

In addition to the lack of radiation exposure, bladder US to assess the lower urinary tract is beneficial for several reasons including being simple, quick, non-invasive, painless and repeatable [27]. US is the most common imaging technique for the bladder. The bladder should be well-distended for optimal visualization but the patient should be comfortable and in the supine position, which may pose a challenge in patients with neurogenic bladders (Fig. 20.3).

US can be used to detect bladder volume pre and post void, bladder mass (although not as sensitive as cystoscopy), stone, foreign body, diverticulum, bladder wall thickness (normal 3–5, <3 mm when distended). The patient can be asked to move laterally to identify mobile versus fixed lesions. A 3.5–5 MHz curved array probe is used. For the anterior bladder wall which is closer to the abdomen, a higher frequency probe may be used. Doppler US may be used to assess the anteromedial ureteric 'jets' which occur approximately 1–3 times per minute [28].

20.1.2.1 Evaluation of the Post Void Residual (PVR)

An elevated PVR in patients with neurogenic abnormality is thought to be a risk factor for upper urinary tract deterioration [9]. The 'gold standard' for assessing PVR is to perform in/ out catheterization. However, this is invasive and poses a risk of UTI and urethral trauma. US is a reasonable, less invasive, alternative for screening neurogenic LUTD patients for elevated PVR. US has been used to assess

bladder volume since reports in 1967 [29]. Assessing PVR urine volumes by means of bladder scanning with portable US devices has found Pearson correlation coefficients between 0.9 and 0.95 when compared to in/out catheterized volumes [29, 30].

As bladder shape may lead to errors in the US estimation of bladder volume, Bih et al. [27] compared the accuracies of various formulas to estimate bladder volume from sonographic measurements. They assessed the impact of bladder shape on bladder volume estimates in 55 SCI patients. Calculated volumes were compared to catheterized and voided volumes. They concluded that the most accurate formula with the least amount of error was: *height* × *transverse depth* × *weight* × *0.7*.

20.1.2.2 Bladder Wall Hypertrophy and Detrusor Compliance

Bladder wall hypertrophy has been associated with neurogenic bladder dysfunction. Measurements of bladder wall thickness (BWT, including the mucosa, detrusor muscle and adventitia), detrusor thickness (DWT, detrusor muscle only) and ultrasound estimated bladder weight (UEBW) may be options to avoid invasive urodynamic testing [31]. These tests are used to assess the severity of lower urinary tract dysfunction and response to treatment. Measurement of BWT is currently a useful research tool, but standardized methodologies are lacking to date [32]. BWT, DWT and UEBW are being investigated as potentially non-invasive options to UDS but are not yet established as routine clinical tests [33, 34].

In the ICI-RS (International Consultation on Incontinence-Research Society) report on Non-invasive Urodynamics, experts agreed on several factors regarding the assessment of BWT. These included: the use of high frequency US probe (7.5 MHz) which has a resolution of 0.13 mm; the use of digital US machines for adequate image enlargement for adequate measurements to be taken; the US appearance of the bladder which consists of hypoechoic detrusor between hyperechoic lines of the mucosa and adventitia; and the use of perpendicular imaging of the bladder wall [32].

BWT/DWT varies depending on the volume within the bladder at the time of US. There is a decrease in BWT/DWT as the bladder volume increases from 50 to 250 cm^3. Above 250 cm^3, the BWT remains stable. All areas of the bladder have similar thickness in an individual, so it does not matter where you image in the bladder. The anterior bladder wall is generally visualized most easily. Children and females have lower BWT/DWT than males. These measurements can be made with abdominal US as well as transvaginal US (Fig. 20.4) [32].

Specifically, in patients with neurogenic LUTD an US frequency of 7.5 MHz is recommended for US assessment but it is uncertain what bladder volume is ideal for BWT/

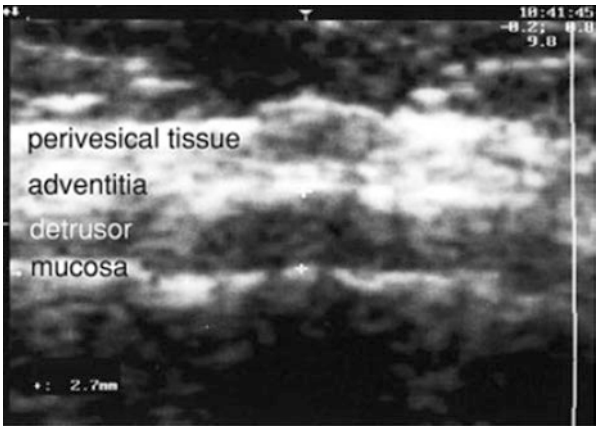

Fig. 20.4 Bladder wall thickness (BWT) and Detrusor wall thickness (DWT) (Needs permission Oelke, 2010)

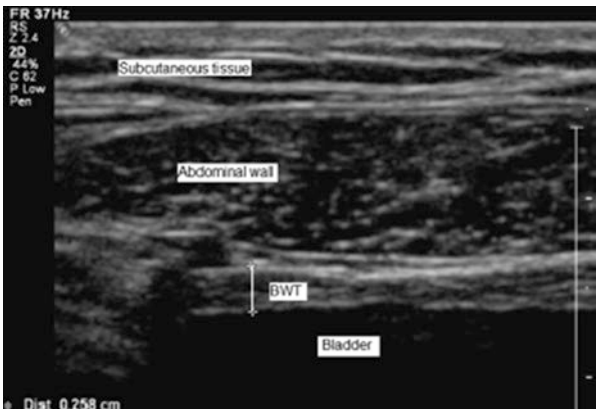

Fig. 20.5 Ultrasonographic measurement of BWT of the anterior bladder wall (Silva 2015-Needs permission Silva 2015)

DWT measurements in this patient population. Silva et al. assessed whether BWT on UD correlated with UDS parameters in SCI patients. They found that BWT was higher in pts with detrusor sphincter dyssynergia compared to those without DSD (4.2 mm vs. 3.6 mm, $p < 0.001$) but that there was no BWT cut-off that could predict an elevated detrusor pressure in the storage phase (ROC = 0.624, 95% CI 0.53, 0.718, $p = 0.01$) (Fig. 20.5) [35]. However, the majority of patients were already on therapy for neurogenic LUTD including CIC and/or anticholinergics. In children with myelodysplasia, Tanaka et al. found a significant difference between BWT in children with and those without urodynamic risk factors ($p < 0.001$). BWT was 3.9 mm ± 1.0 mm compared to 2.4 ± 0.7 mm in 16 children with unfavourable UDS compared to 41 children with favourable UDS, respectively [36].

Calculation of the UEBW has also been described using transabdominal US [37]. UEBW has been used as a means to identify obstructed (UEBW >35 g) versus non-obstructed bladders (UEBW <35 g) in Japanese patients. In addition, a

cut off of 40 g has been reported to have a diagnostic accuracy of 96% for poorly compliant bladders.

Bayat et al. assessed the correlation of US bladder vibrometry (UBV) and bladder compliance detected on UDS. UBV uses acoustic radiation force to excite transient waves in tissues. UBV is able to assess parameters of elasticity and viscosity based on mathematical assessments along the bladder wall. The results are reported in terms of the bladder wall's modulus of elasticity, as well as Lamb wave group velocity. Early studies show that velocity increases at higher volumes, however the rate of the increase depends on bladder compliance. For a noncompliant bladder, a rapid change in velocity is expected while a compliant bladder shows a gradual increase in velocity. The authors found that using UBV can monitor changes in bladder wall properties that correlate well with detrusor pressure measurements (Pearson correlation 0.9–0.99). They suggest this novel technique is a reliable and cost-effective tool for assessment of the bladder wall in a non-invasive fashion. This is not yet available for routine clinical use [38].

Similarly, Sturm et al. recently reported the use of ultrasound shear wave elastrography (SWE) as a novel method of assessing bladder compliance in children with neurogenic LUTD. Ultrasound SWE is an imaging modality to look at the mechanical properties of soft tissue. The authors found that the mean shear wave speed of the anterior wall significantly correlated with detrusor pressure throughout bladder filling and the shear wave speed measurements were able to differentiate compliant vs. noncompliant bladder [39].

To date, the use of BWT/DWT, UEBW, UBV and US SWE for predicting lower urinary tract dysfunction in neurogenic patients is not yet routine clinical practice and study results are influenced by a lack of standardized protocols. In the future, these procedures may become useful tools for avoiding invasive UDS testing.

A comprehensive review of the literature on this topic was done by Bright et al. [40].

20.1.2.3 Bladder Stones

US of the lower urinary tract can also detect bladder stones which occur in a large number of patients with neurogenic LUTD. Trabeculation of the bladder may also be detected by US and has been found in 35.1% of 1005 SCI patients over 6 years. The presence of bladder trabeculation was associated with a higher rate of bladder/renal calculi and renal atrophy when compared to patients without bladder trabeculation ($p = 0.001$) [10].

20.1.2.4 Sphincteric Abnormalities

Fowler's syndrome is the development of urinary retention due to the inability of the external sphincter to relax during voiding. The cause of Fowler's syndrome is uncertain but it occurs in young woman (20–30 years) and there is no underlying neurological disorder to account for the symptoms. Transvaginal US has been used to assess the volume of the external sphincter muscle in women with complete or partial urinary retention consistent with Fowler's syndrome. Wiseman et al. [41] found an increase in maximum urethral sphincter volume in these women compared to women without this abnormality (2.29 ± 0.64 vs. 1.62 ± 0.32 cm^3, $p < 0.001$). They concluded ultrasound measurement of sphincter volume was helpful to detect hypertrophy of the striated sphincter resulting from sustained overactivity. Operator variability in this measurement has restricted its usefulness in the diagnostic algorithm for these patients.

20.2 CT Scanning for Both Upper and Lower Urinary Tract: Reconstruction

Computer Tomography (CT) or Computer Axial Tomography (CAT) is now often utilized in the evaluation of the upper urinary tract including patients with NLUTD after the first line evaluation with US and it has replaced intravenous urography (IVU) almost entirely. CT is a computerized X-ray imaging technique in which a thin beam of X-rays, quickly rotated around the body, generating cross-sectional images, "slices" of the body. Pictures can then be reconstructed in 2D along any plane or in 3D images. Most modern CT machines take continuous pictures in a helical (or spiral) fashion rather than taking a series of pictures of individual slices of the body, produces better 3D pictures of areas inside the body. In general, intravenous contrast medium is required to highlight specific anatomic characteristics, however CT scan can be also used in patients with poor renal function without contrast medium. The urine, without the contrast, can delineate the collecting system and detects hydronephrosis if present, reducing the need for contrast agents. Image reconstruction in CT is a mathematical process that produces tomographic images from series of X-ray projection data. Image reconstruction has a significant impacts on image quality and reduction of the radiation dose. Two major techniques of reconstruction methods exist, analytical reconstruction (AR) and iterative reconstruction (IR) [42]. The reconstructive logarithm is usually incorporated into CT equipment and can be adapted by user for different images application.

20.2.1 Safety

The routine CT scan of the abdomen and pelvis without contrast had the median effective dose (15 mSv [IQR, 10–20 mSv]), whereas a multiphase abdominal and pelvis

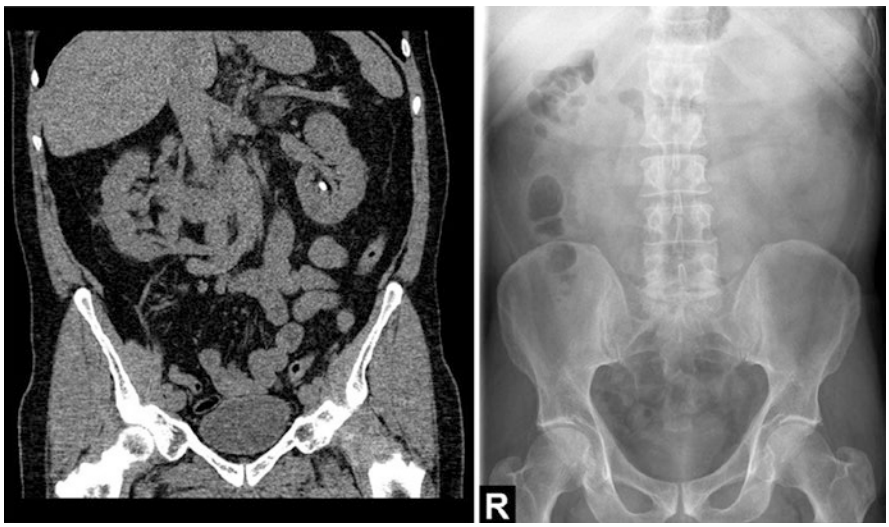

Fig. 20.6 Radiolucent stone on KUB visualize on CT examination

CT scan had the highest median effective dose (31 mSv [IQR, 21–43 mSv]) [43]. It is reported that a CT scan may be associated with an increase in the risk of cancer of approximately 1 in 2000 [44, 45]. Berrington de González [46] estimate that approximately 29,000 future cancers could be related to CT scans performed in the U.S. in 2007. Optimizing the radiation dose has been strongly encouraged [47].

20.2.2 Indications

CT can be utilised in evaluation of the UUT in NLUTD, particularly in case of unclear diagnosis of hydronephrosis or stones on US. If there is an indication to do CT for stone evaluation, stone protocol can be implemented which reduces amount of radiation (Fig. 20.6).

An extensive review of the three-dimensional reconstruction of structures and organs, post-surgical evaluation of the organs of the pelvis and abdomen scanned by CT, creating a pseudo-virtual reality (VR), has been published by Stenzl et al. (Fig. 20.7) [48]. They also published experience with 50 orthotopic bladder (Fig. 20.4) substitutions and 3D images [49]. It was found useful in delineating ileal loop anatomy and ureteric anastomosis. This technique in combination with urodynamics, was also implemented to evaluate neobladder function [50].

Another report applied virtual reality 3D CT images to evaluate bladder pathology in 18 patients, compared to the conventional cystoscopy. The different urinary bladder disease, consisted of 11 tumors, 3 diverticula, 2 trabecular changes and 2 stones has been evaluated. The images were excellent and there were no false positive findings [51].

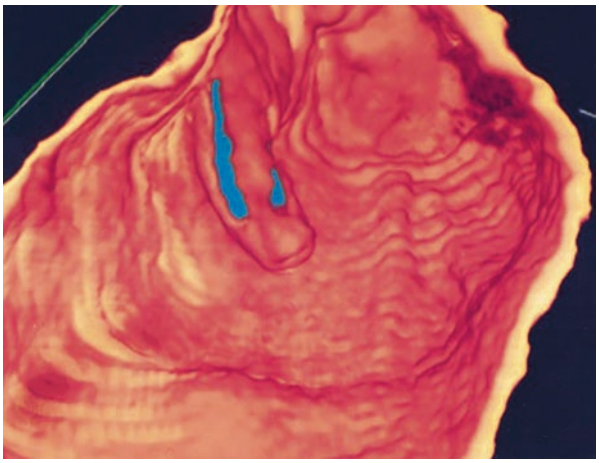

Fig. 20.7 Virtual reality endoscopy of an orthotopic neobladder. This technique enables an endoscopic 'fly-through' effect not only of the pouch, but also of the antireflux nipple (depicted here), afferent ileal limb and ureters, which cannot easily be reached by endoscopy **[Stenzl 1999-needs permission]**

20.3 MRI/MRU for Both Upper and Lower Urinary Tract

Magnetic resonance imaging (MRI) is an imaging technique creating anatomical pictures including physiological processes within the body structures. MRI scanners use strong magnetic fields, radio waves, and field gradients to generate images mostly from the emission of the hydrogen atoms. MRI has some advantage over other tests that include contrast media (gadolinium contrast agents) which is relatively free of allergic reactions. Imaging can be performed along any plane and pictures can then be presented in a 2D or 3D dimensions. Some concerns was raised regarding using MRI

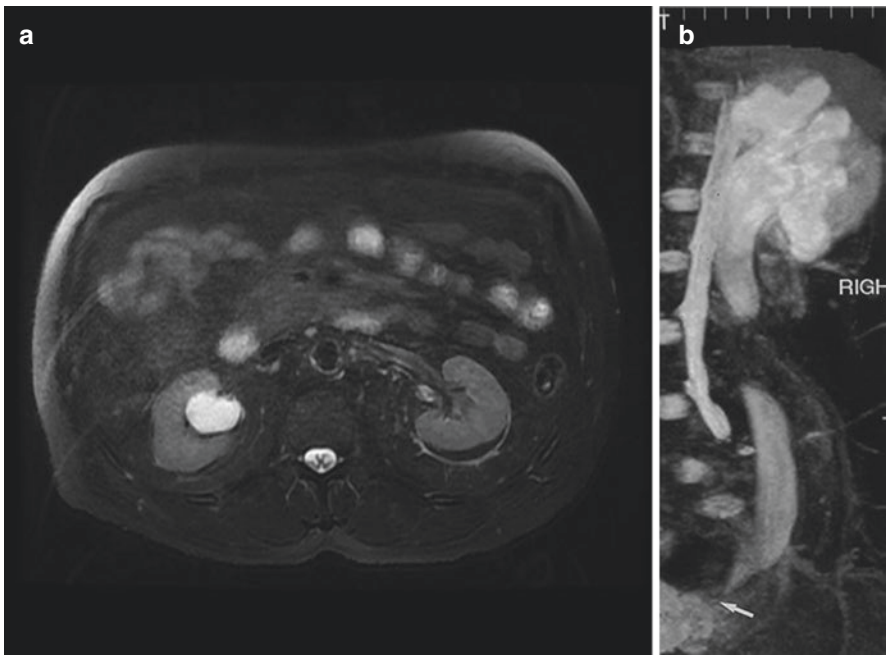

Fig. 20.8 (**a**) MRU transverse showing hydronephrosis (own picture). (**b**) MRU (MIP projection) showing hydronephrotic changes of the right kidney and a dilated right ureter with a stricture at its lower end (arrow). Cortical scarring of the kidney is also present **[Shipstone 2002-needs permission]**

contrast media in relationship to poor renal function and nephrotoxicity [52]. The higher doses have been linked to the development of nephrogenic systemic fibrosis (NSF) [53]. MRI has been recently utilized to evaluate hydronephrosis, urinary tract anomalies and pelvic floor anatomy [54] as an alternative to intravenous urography (IVU) (Fig. 20.8a) and supplementing CT imaging (Fig. 20.8b) [55]. This has been especially helpful in patients with NLUTD with spinal deformity when other technique may not be ideal to evaluate obscured kidneys [55]. There is one report that MRU carried out in healthy young adult volunteers with a full bladder allows improved visualization of the upper tracts. Although the ability of magnetic resonance urography (MRU) to detect stones and abnormal calcification in the urinary tract has been disappointing [56].

MRI has been also found to be useful in patients with urinary diversion. T2-weighted MR urography alone has high sensitivity, specificity and accuracy, can provide additional information and does not require intravenous contrast medium (Fig. 20.9). The results can be obtained in 3–5 min [57].

Ultra-Fast Image Acquisition and MR Sequences has been introduced to evaluate female pelvic organ movements [58, 59]. These sequential images are acquired once per second, either as a series of images covering the entire pelvis (static imaging) or repetitively in one plane while the organ(s) are moving (dynamic imaging). Real Time (rt) MRI has been also utilized in men to investigate the interactions between the bladder, urethra, pelvic floor and the function of the prostate during 'normal' voiding [60]. The role of this technique has not be established in NLUTD.

MRI Videurodynamic concept has been introduced to evaluate function and morphology of the system at the same time [61]. This initial publication is combining fast imaging MRI of pelvis and urodynamics in patients with stress urinary incontinence. The idea can be extrapolated to the NLUTD as well however no reports has been published.

20.4 Evaluation of the CNS in NLUTD

Comparison of the average change in activation between previously reported healthy controls [62] and patients with multiple sclerosis showed predominantly stronger, more focal activation in the areas of activation in regions associated with executive function (frontal gyrus), and emotional regulation (cingulate gyrus), and more diffused activation in the motor control (putamen, cerebellum and precuneus) (Fig. 20.10) [63].

20.4.1 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging or functional MRI (fMRI) is a neuroimaging that measures brain activity by detecting changes associated with blood flow. fMRI has been used as a research tool in patients with overactive bladder but

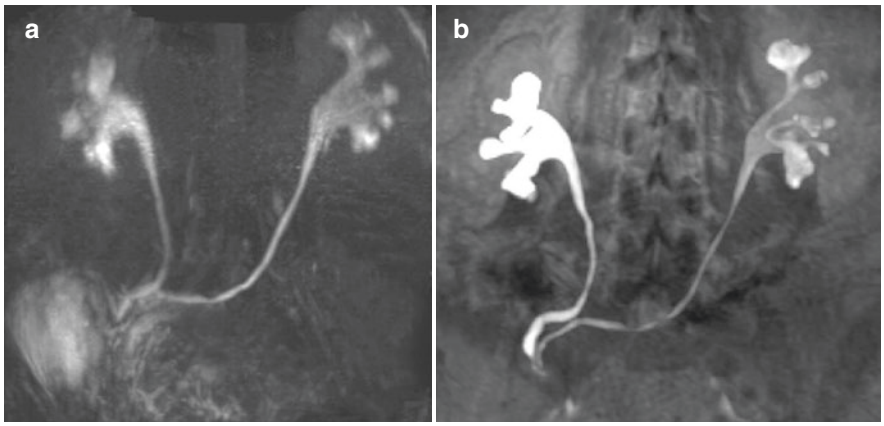

Fig. 20.9 A 54-year-old male patient with cutaneousureterostomy. Coronal maximum intensity-projection MR urography images obtained from three-dimensional (3D) T2 turbo spin echo (**a**), and excretory phase 3D T1-weighted (**b**) sequences show bilateral intrarenal collecting systems and entire courses of ureters with cutaneous anastomoses **[Battal 2011 needs permission]**

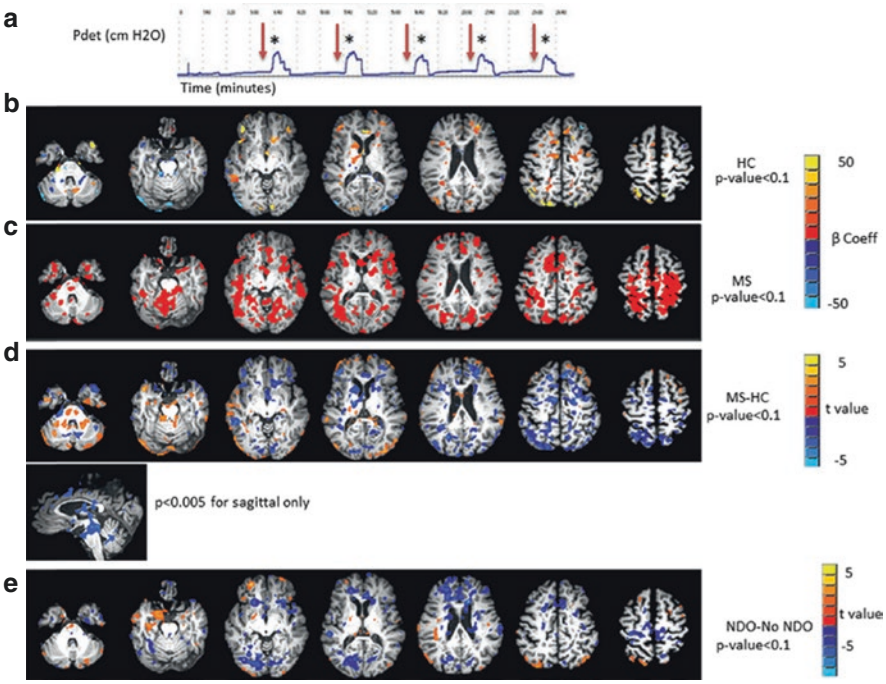

Fig. 20.10 BOLD activation signals at strong desire to void. (**a**) UDS tracing of 5 cycles. Pdet, detrusor pressure. Arrows indicate voiding initiation. (**b**) Group analysis of HC. (**c**) Group analysis of patients with MS. (**d**) Subtraction between patients with MS and HCs demonstrates predominantly lower activation in patients at strong desire to void. (**e**) Trend in patients with MS with vs. without demonstrable NDO. Warmer colors represent increased activation in patients with MS. Cooler colors represent decreased activation in HCs **[Khavari 2017-needs permission]**

only few studies has been conducted in SCI patients with neurogenic LUTD [64].

20.4.2 A Single-Photon Emission Computerized Tomography (SPECT)

SPECT utilize a nuclear medicine tomographic imaging technique a gamma-emitting radioisotope and presents as a 3D image. In most of the cases, marker radioisotope is attached to a specific ligand to create a radioligand, whose properties bind it to certain types of tissues. Urinary dysfunction found in idiopathic normal-pressure hydrocephalus (iNPH) assessed by single-photon emission computed tomography [123I]-IMP SPECT and statistical brain mapping showed closed relationship with right frontal hypoperfusion. While secondary incontinence can result from gait disturbance or dementia, there may also be a neurogenic mechanism underlying urinary dysfunction, which is a significant burden in patients with iNPH and their caregivers [65]. SPECT brain imaging with special reference of bladder function, was performed in patients with multiple system atrophy (MSA). The test showed decrease in tracer activity in the cerebellar vermis during urinary storage and micturition is contributing to the micturitional disturbance in this disorder.

20.4.3 Positron Emission Tomography (PET)

Neuroimaging-**positron emission tomography (PET)** detects radiation from a radioactive tracer injected intravenously, to evaluate organs and tissues function. Brain

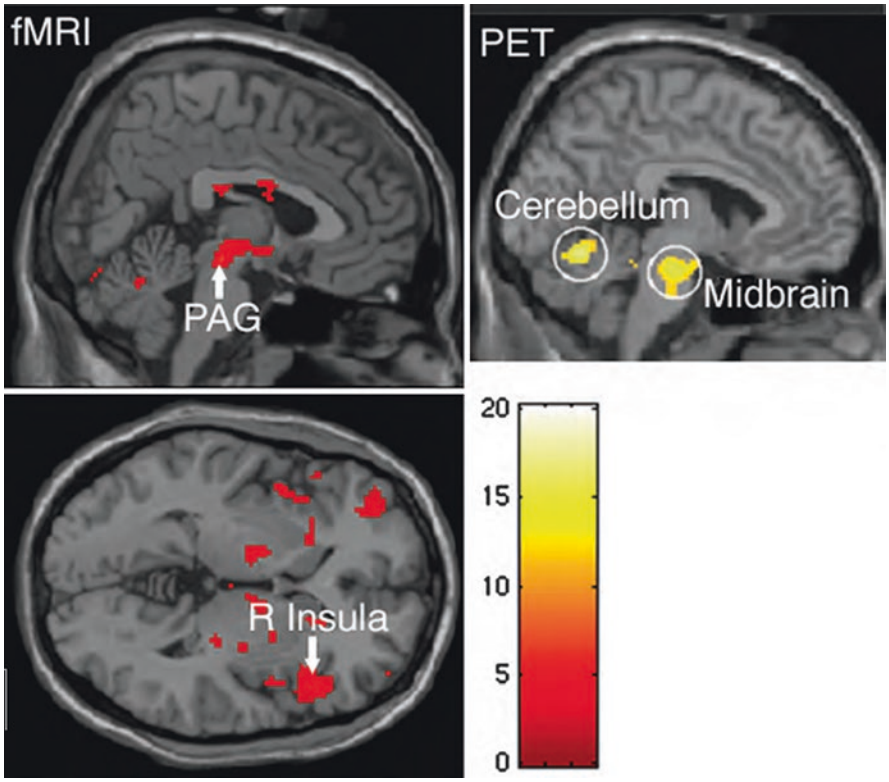

Fig. 20.11 PET imaging showed that with SNM afferent activity reached the midbrain [67, 69] and more recently with functional magnetic resonance imaging (fMRI) the PAG and right insula showed activation [68] **[DeGupta 2005 & Griffith 2010 needs permission]**

responses to bladder filling are abnormal in Fowler syndrome (FS), especially when assessed by fMRI [66]. PET offers less comprehensive but consistent results [67]. With rapid filling, deactivation instead of activation in widespread brain areas is reflected in poor sensation and inability to void. SNM partially but incompletely normalizes this abnormal brain activity and thus improves sensation and voiding. However, it does not reverse the primary abnormality, the urethral sphincter overactivity [68].

There are limited reports on using PET studies in other NLUTD, mainly in Parkinson's disease [69, 70]. Based on the PET and FMRI study it is suggested that Sacral Neuromodulation (SNM) probably restored voiding in women with FS by resetting brainstem function (Fig. 20.11) [66].

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Renal Function Evaluation

21

Nuno Grilo and Brigitte Schurch

21.1 In Adults

Renal function evaluation is a key factor in the long-term follow-up of patients with neurogenic bladder dysfunction. It is as crucial as complex, since many of the tests available nowadays, lack accuracy, particularly in this group of patients [1]. Lawrenson et al. showed that patients with neural tube defects have an eightfold greater risk of developing renal failure, whereas spinal cord injury patients present a fivefold greater risk [2]. As it would be expected, this risk increases exponentially with age. In multiple sclerosis, the overall risk of upper tract damage is considerably lower, being almost similar to the general population [3–5]. Whatever the neurological condition, an accurate renal function evaluation is then key to early diagnosis and follow-up of various kidney diseases in this group of patients.

At the moment, there are no clear guidelines on the frequency of renal function check-ups in neurogenic patients. European Association of Urology states, upper urinary tract should be assessed at least every 1–2 years, and this interval should be significantly shorter in high risk patients [6]. The French recommendations are that, in patients with neurogenic bladder, renal function should be evaluated annually by measurement of 24-h creatinine clearance associated with ultrasound of the urinary tract [7].

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21.1.1 Available Tests

The most accurate ways to measure GFR are by clearance of inulin or radiopharmaceuticals, but these aren't widely available [8].

There are numerous widely available different tests to measure/estimate glomerular filtration rate (GFR), but not all of them are ideal for the neurologic patients.

21.1.1.1 Creatinine

The most globally used marker of GFR is, without any doubt, plasma creatinine. Creatinine is freely filtered at the glomerulus and is not reabsorbed, 15% being still actively secreted in the tubules. This is a marker that has the advantages of presenting a stable plasma concentration throughout the day, being practical to measure and rather inexpensive. Unfortunately, it has also the inconvenient of being influenced by far too many factors (age, sex, ethnicity, body composition, diet, muscle breakdown and various medications).

In most neurologic patients, body composition is hugely disturbed with an important loss of lean body mass [1]. As weight is a crucial part of creatinine GFR-estimation formulas, these tend to dangerously overestimate renal function in neurologic patients, which can lead to a more passive caring, possibly delaying treatments patients should promptly benefit, in order to protect upper urinary tract.

In order to improve creatinine accuracy on estimating renal function, creatinine clearance can be used.

Creatinine Clearance

Joining a timed 24 h urine collection to the serum creatinine measurement, allows to better estimate GFR:

$$\text{Creatinine clearance} = \left(\text{urine creatinine} \times \text{volume}\right) / \text{serum creatinine}$$

Because of tubular secretion of creatinine, this formula still tends to overestimate true GFR.

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_21

This error is nevertheless of a fairly stable magnitude, allowing creatinine clearance to be an acceptable method for evaluating individual renal function alterations [8].

The main reason why creatinine clearance is not used more often, is that urine collection over 24 h is bothersome and also an individual 25% daily variation has been observed with this method [9]. Also, the high prevalence of incontinence in the neurogenic bladder population, means that in order to correctly collect 24 h urine, many of these patients with indeed need bladder catheterisation.

Creatinine Based Formulae

Several different creatinine based formulas were developed over the past decades in order to estimate glomerular filtration rate. Nowadays the utilisation of the MDRD, Cockroft-Gault equations, or the more recent CKD-EPI formula are recommended.

Cockcroft-Gault:

Modification of Diet in Renal Disease (MDRD):

$$175 \times plasma\ \ creatinine^{1.154} \times age^{0.203} \left(\times 0.742\ \ if\ \ \ female; \times 1.21\ \ if\ \ \ black\right)$$

Chronic Kidney Diseases Epidemiology Collaboration (CKD-EPI):

For women with a plasma creatinine ≤ 0.7
For women with a plasma creatinine >0.7
For men with a plasma creatinine ≤ 0.9
For men with a plasma creatinine >0.9

Michels et al. compared all these three equations, showing that all of them are biased by age. The CKD-EPI and MDRD formulas are also influenced by GFR, and the Cockcroft-Gault equation is additionally influenced by body weight and BMI. In general, CKD-EPI appears to give the best estimation of GFR, being slightly better than that of MDRD [10]. Unfortunately, this study has excluded all neurologic patients, and to our knowledge, no other study has compared these three equations in the neurologically ill population.

While being reasonably accurate to estimate renal function, these formulae may be defective in patients with neurogenic bladder, since they are based on the plasma creatinine measurement. These patients have varying lean muscle mass loss that is proportionally greater than fat mass loss. The change in proportion between the various components of body mass means that serum creatinine will be considerably lower in this group than in normal fit patients.

To sum up, it is important to say, that while a single value of creatinine may highly overestimate renal function in a neurologic ill patient, it remains a good parameter to assess evolution of renal function over time.

21.1.1.2 Urea

Due not only to being influenced by many different factors, as high-protein diet, dehydration, corticosteroid therapy and tissue breakdown, but also because 40% and 50% of filtered urea may be reabsorbed out of the tubules, plasma urea is a much less reliable marker of GFR than plasma creatinine, and for this reason it should not be used alone in the assessment of renal function [11].

21.1.1.3 Cystatin C

Cystatin C is produced at a fixed rhythm by all nucleated cells and is freely filtrated by in the nephron. Its biggest advantage is that it seems to be independent from age, sex, diet, lean body mass and weight [12]. For this reason, plasma cystatin C seems to be a better indicator of GFR than plasma creatinine and urea.

Nevertheless, it is important to know that plasma cystatin C can be overestimated in HIV and cancer patients as well as in those under glucocorticoid treatment [13–15].

Recently, Mingat et al. have published a multicentre prospective study comparing the different methods of renal function evaluation in patients with neurogenic bladder dysfunction. This study has shown a superiority of CKD-EPI cystatin C equation, rather than creatinine-based equations in this group of patients. This equation has shown to be twice as precise than 24-h creatinine clearance, the latter systematically overestimating GFR in this population [16].

Cystatin Based Formula

Chronic Kidney Diseases Epidemiology Collaboration (CKD-EPI):

$$127 \times plasma\,cystatin \times age\left(\times 0.91\ if\ \ female; \times 1.06\ if\ black\right)$$

21.1.1.4 Inuline Clearance

Inuline is an exogenous substance, considered ideal in evaluating GFR. Its use in daily practice is impossible, due to its elevated cost and very time consuming process. The procedure consists in a bolus injection of inulin, followed by collection of regular blood and urine samples over several hours for inulin estimation. This is only compatible with investigation studies where very precise estimation of GFR is key [8].

21.1.1.5 Radioisotopic Methods

Renal imaging in nuclear medicine remains an important method of renal function evaluation.

There are two different techniques that can be performed, each other with specific aims.

Dynamic Renal Imaging

Radiopharmaceuticals used:

^{123}I-orthoiodohippurate (OIH)
^{99m}Tc-diethylenetriaminepentaacetate (DTPA)
^{99m}Tc-mercaptoacetyltriglycine (MAG3)

To perform a diuretic renography, patient should be well hydrated and have recently voided. Oral hydration of 15 mL/kg during the 30 min before renography is advised [17]. The patient should void just before the exam, in order to decrease the possibility that he needs to void during the exam and also to avoid a full bladder, that may delay upper tract emptying, biasing the results. Injection of a diuretic, can be done before, at the same time (so-called "F + 0" method for furosemide at 0 min) or after tracer injection (generally 15 min afterwards, the so-called "F + 15" method) [18].

The diuretic renography allows evaluation of differential renal function, but with a lower sensitivity than a static renography. Differential renal function is the result of the contribution of each kidney to total renal function, which is normally comprised between 45% and 55% [19].

A differential renal function below 40% or a decrease of differential renal function of more than 5% on consecutive studies should be taken into account as a possible renal function deterioration, possibly due to obstructive uropathy [17].

Nevertheless, one should be very careful when making this kind of conclusions based on the scintigraphy alone, since the apparent pejoration of function of one kidney over time, can in fact be due to the compensation of the contralateral one [17]. Relying exclusively on radioisotopic methods to determine absolute renal function is not recommended, and clearance techniques based on blood sampling remain the gold standard [20], although some centres have developed reliable methods to measure individual kidneys function indices (the so-called accumulation indices or AI). Accordingly, cystatin based equation seems to be preferable in estimating absolute renal function in neurologic patients.

Static Renal Imaging

Radiopharmaceuticals used:

^{99m}Tc–dimercaptosuccinic acid (DMSA)

Scintigraphy with DMSA is a simple and noninvasive method that requires imaging 2–4 h after intravenous injection. It allows for evaluation of parenchymal scarring, with a sensitivity from 80%, but does not allow differentiation of acute pyelonephritis from chronic parenchymal defect, unless a 6-month interval would have passed since the last episode of upper urinary tract infection; in that case, a photopenic defect would correspond to parenchymal scarring [21, 22].

Static scintigraphy with DMSA is superior to dynamic renography in evaluating renal scarring, but carries a greater radiation burden [23].

21.2 Conclusion

As previously stated, accurate evaluation of renal function in neurologic patients, specially in neural tube defects and spinal cord injury patients is crucial. Regular check-ups of renal function are then advisable and their frequency should take into account the individual risk of each patient for renal function deterioration.

Creatinine remains a valid option in monitoring renal function. Since its absolute value is for most part inaccurate in the neurogenic bladder population, it is its evolution over time that is most clinically relevant.

Cystatin C, along with its CKD-EPI formula is a welcome new weapon in the arsenal of renal function evaluation, that seems to be especially interesting in the neurogenic bladder patient.

Radioisotopic methods, remain key in the evaluation of partial renal function, renal damage and urinary flow.

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Endoscopic Evaluation of Neurogenic Bladder

22

Jürgen Pannek

Although video-urodynamic examinations are the most important diagnostic tool for evaluation of neurogenic lower urinary tract dysfunction (NLUTD), endoscopy is an important additional procedure in a certain subset of patients.

Within the last decades, the survival rates of patients with spinal cord injury have improved considerably. In addition, the age at spinal cord injury (SCI) onset has increased. As a consequence, the number of patients with SCI and subsequent NLUTD being older than 50 years is rising. Therefore, the incidence of morphologic changes, e.g. urothelial carcinoma of the bladder, which is increasing with age, is also increasing in patients with NLUTD. Today, there is an ongoing debate if bladder tumors are more frequent in patients with SCI compared to the general population [1]. The most recent data show that bladder tumors in patients with NLUTD are detected in a more advanced stage [2], which may at least in part be due to the paucity of specific symptoms, as microhematuria in this patients is common, but often occurs in patients using intermittent catheterization, indwelling catheters or presenting with bacteriuria/urinary tract infection. Due to the above mentioned intuitive explanations for microhematuria in these patients, endoscopic evaluation is not regularly performed in each patient with erythrocytes in the urine, which may lead to a delayed detection of bladder tumors. The recommendations from recent publications differ considerably, some recommending no screening for bladder tumors, others opting for regular cystoscopy in every patient with NLUTD [3, 4]. A possible practical approach is to restrict endoscopic evaluation to patients at risk for bladder tumor, especially those with long-term indwelling catheters. The time-span to bladder cancer development in this group of patients, however, is unclear, and recommendations concerning endoscopic screening after catheter insertion vary between 5 and 16 years [5]. Furthermore, the diagnostic value of endoscopy in patients with long-term indwelling catheters has been questioned, as these catheters produce morphologic alterations that cannot be macroscopically distinguished from bladder tumors [6]. A possible way to improve the diagnostic value is to combine endoscopic evaluation with bladder wash cytology [7].

Recurrent urinary tract infections are frequent in patients with NLUTD. Besides functional reasons, also morphologic causes for infection, like stones, foreign bodies, diverticula or fistula, should be excluded. Therefore, endoscopy is indicated if other imaging techniques are inconclusive.

Endoscopy is also indicated in patients that are performing reflex voiding after sphincterotomy if residual urine is elevated. By endoscopy, sphincter sclerosis as a long-term sequelae of sphincterotomy can be assessed in order to decide if re-sphincterotomy is indicated.

It is, however, of utmost importance to consider that patients with a spinal lesion above Th6 frequently suffer from autonomic dysreflexia (A.D.), which is a consequence of provoked uncontrolled sympathetic activity, leading to severe and rapid paroxysmal hypertension and bradycardia. A.D. is potentially life-threatening, as it can lead to e.g. convulsions, intra-cerebral bleeding, or pulmonary edema [8]. As A.D. can be triggered by endoscopic procedures, there has to be a clear-cut indication for such an intervention, especially in patients with a level of lesion above Th6. Therefore, endoscopic evaluation should not be performed as a routine screening procedure in each patient with NLUTD.

22.1 Endoscopy After Bladder Augmentation

After bladder augmentation, patients have a risk of developing bladder calculi or bladder tumors [9, 10]. A recent systematic review demonstrated that the mean time between surgery and development of a bladder tumor is 19 years, and the vast majority of tumors presented after 10 years [9]. Therefore, endoscopy in this patient group

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_22

should be performed if a stone/tumor cannot be excluded by imaging, or as a bladder cancer screening. Although the efficacy of cystoscopy surveillance is under debate [9], currently, no better option exists. Therefore, cystoscopy is advised after augmentation cystoplasty, at latest 10 years after surgery.

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Part VIII

Treatment

An Overview of Treatment

23

Julian Shah

23.1 Primary Aim of Treatment of NLUTD and Their Priorities

23.1.1 Protection of the Upper Urinary Tract

After the development of a neuropathic bladder the principle aim should be to maintain a patient's bladder function as close to normality as possible. The change in function of the bladder with neurological disease will much depend upon the nature of the disease whether acute or chronic, long-standing or congenital, or of gradual or sudden onset. When bladder function changes with neurological dysfunction the principle effects will be either retention, incontinence or both.

The management should be directed to preserving the storage and emptying function of the bladder so there is no detriment to the kidneys and provide continence whenever possible.

The normal bladder will store under low pressure and empty to completion.

Thus, the very simple rules of bladder management for patients with neurogenic bladder dysfunction are:

(a) Low pressure storage and
(b) Complete bladder emptying.

If the bladder can be made to store under low pressure whatever the neuropathic background then there should be little or no risk to the upper urinary tract.

The principle concern in modern management has been to avoid any long-term damage to the kidneys. In this modern era it should be rare to encounter renal dysfunction which has been caused by bladder dysfunction.

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With the arrival of routine urodynamic studies and an understanding of the relevance of the effect of bladder pressure on the upper urinary tract, which was based on the observation by McGuire et al. [1] that 80% of patients with intravesical pressures greater than 40 cm H_2O at urinary leakage (detrusor leak point pressure [DLPP]) had reflux and/or hydronephrosis lead to more careful supervision of patients with neuropathic bladders. It has been found that sustained intravesical pressures greater than 20 cm H_2O may create risk to the upper urinary tract [2].

Since we have been able to understand the relevance of urodynamic investigations and how the pressure in the bladder can affect the upper urinary tract we are now able (or should be able) to ensure that the patient is protected from any deterioration in renal function.

Thus, maintaining low pressure storage within the bladder is a critical component of any patient's management. However the only way that one can know that the patient's bladder is "safe" is with urodynamic testing.

Thus urodynamic studies have become the mainstay of investigation of the bladder and the supervised and controlled management of any patient with neuropathic bladder dysfunction.

To ensure that problems do not develop in the long term any patient with a neuropathic bladder, long term follow up is required. This is part of the guidelines of both the BAUS and the EAU [3]. The EAU guidelines are stringent in recommending meticulous follow-up which depends upon the underlying pathology. A scan of the urinary tract is recommended every 6 months and detailed investigation including urodynamics every 1–2 years. Although we should all accept that this is an ideal this is rarely met in clinical practice. It is unlikely than any country can provide this level of care because of the volume of work, the paucity of specialist urologists and facilities to conduct these investigations. Thus when there are limited facilities available to investigate and manage every patient with a neuropathic bladder on an annual basis those specifically at risk should be managed (Table 23.1). This is very comprehensively covered in the

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_23

Table 23.1 Definition of risk factors in strategy 3

Definite risk factors	Probable risk factors
• MS duration beyond 15 years	• Detrusor-sphincter dyssynergia
• Indwelling urinary catheter	• Age over 50 years
• Ample uninhibited contractions of the detursor	• Male sex
• High detrusor pressure	

Taken from NICE Guidelines [4]

NICE Guidelines—Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological; disease [4]. Recommendations are made at to which patients to should be more closely followed and those that do not need such close supervision. These guidelines are very comprehensive and should be recommended reading for anyone interested in this field.

The time to develop upper tract dilatation can often be long and may take many years. In an unpublished study that we conducted at the RNOH we noted that it took a mean of 8 years until renal tract changes were noted after a patient had developed a spinal cord injury. These problems usually arose in patients who had had management of the required standard but patient factors rather than medical factors, for example the patient's failure to return for follow up care, that led to the situation deteriorating without there being a knowledge of the changes occurring.

23.1.1.1 Videourodynamics

We can achieve the best outcome for our patients by understanding the dynamics of the bladder with urodynamic testing. The video urodynamic study is the gold standard and should remain so since this allows us both the assessment of bladder pressure during filling and "voiding" and a view of the bladder appearance, the outlet and the presence or absence of reflux. The findings are essential when determining the next steps in management.

Thus, after the development of a neuropathic bladder an understanding of the base line dynamic function is important and then attention should be turned to the relationship between storage and emptying. The base line urodynamic study should be part of the protocol in a spinal injury centre or be the first study performed in a newly referred patient whose disease has been present for many years.

23.1.1.2 Bladder Emptying

Although approaching bladder emptying first may seem perverse, it is bladder emptying which often predicts the management of the bladder in general.

If the bladder can empty naturally with "balanced" voiding then dealing with the storage of urine becomes the main problem.

If the bladder does not empty naturally then emptying of the bladder is ideally achieved by intermittent self catheterisation. This should be the primary management for bladder emptying when the bladder cannot empty naturally.

Table 23.2 Reasons for not being able to self-catheterise

• Hand disability seen in high level spinal cord injury and where there have been injuries affecting hand function
• Females with disability
• Obesity
• Pain on self-catheterisation
• Lack of willingness of behalf of the patient

Intermittent catheterization is not always possible. There are a number of reasons why intermittent catheterization may be impossible or the patient may chose not to wish to self-catheterise (Table 23.2).

When self-catheterisation is not possible long-term indwelling catheterization may be necessary. Long-term catheterization should be by suprapubic catheterisation.

The use of a sphincterotomy to alleviate destrusor sphincteric dyssynergia in the male has become very uncommon in the modern era. It still may have a place in patients with significant detrusor sphincter dyssynergia and high pressure voiding, who are prepared to wear conveen drainage. Thus it is only applicable to male patients.

23.1.1.3 Bladder Storage

The most important component once the emptying of the bladder has been decided is to maintain low pressure bladder storage. This is achieved using the following techniques:

- Anticholinergic medication
- Intravesical Botox
- Augmentation ileocystoplasty
- Sacral anterior root stimulation plus dorsal rhizotomy

Maintaining low pressures within the bladder whether the patient does intermittent self catheterisation or has long term catheterisation should protect the upper urinary tract from deterioration.

Three components contribute to upper tract deterioration:

1. High pressure within the bladder
2. Bladder wall thickness causing ureteric obstruction where the ureters come through the bladder wall
3. Vesico-ureteric reflux
4. Or a combination of reflux and obstruction which can occur in the same patient.

Reflux can occur in association with obstruction in the occasional case and this can be picked up by urodynamic studies and upper tract imaging.

Provided the bladder is kept under low pressure and the patient is able to empty satisfactorily there is no reason why upper tract deterioration should occur. In the modern era

where supervised long-term management is provided this is very unusual. In our own experience renal dysfunction has only been seen in a small number of patients over 30 years. Problems have usually been due to the patient's non-compliance. Provided annual follow up of the patient is conducted along with appropriate imaging there is no reason why upper tract deterioration should occur or when changes occur action can be taken to investigate the cause and treat appropriately.

23.1.1.4 Need for Follow-Up

As previously discussed the need for follow-up is determined by the availability of the facilities and personnel to provide such care. The ideal would be to provide follow-up management for all patients as per the guidelines but usually has to be applied to those most considered at risk.

Annual follow up should consist of at least an ultrasound scan of the urinary tract with an assessment of bladder emptying and a consultation. An abdominal X Ray is not necessary (see NICE guidelines).

Urodynamic studies should be repeated as necessary, not necessarily every year but certainly when appropriate particularly if there is any risk that the patient has had or may develop high pressure bladder dysfunction and to follow-up treatment which affects intravesical pressure.

It has not been our routine to perform a MAG 3 scan in patients who have suffered a spinal cord injury but some units do this. There is no criticism of using MAG 3 scanning but an ultrasound scan of the urinary tract, which demonstrates normal and non-dilated kidneys should be sufficient if the serum creatinine is within the normal range. If any dilatation is discovered it is recommended to proceed to a MAG 3 scan or a CT urogram according to the needs.

23.1.2 Preservation of Continence

Urinary continence is a component of normal bladder function. Patients, who suffer a neurological disease that affects the bladder, may develop urinary incontinence. Incontinence causes distress and can cause problems with management particularly if the patient becomes bathed in urine that could affect the healing of other sites (with the potential for poor skin quality and the development of pressure sores). For any patient, who has a neuropathic bladder incontinence is a devastating complication. Thus, an attempt should be made to ensure that the patient remains continent.

The causes of incontinence after a neuropathic bladder dysfunction are:

1. Neurogenic detrusor overactivity
2. Overflow incontinence due to retention
3. Stress urinary incontinence
4. A combination of factors

The understanding of the causes of incontinence of course is essential and will be discovered by taking both a history and examination and by performing urodynamic testing. The simplest problem to resolve is that of overflow incontinence, which usually can be resolved by draining the bladder effectively by intermittent catheterisation or other means. If retention is discovered which is associated with incontinence once intermittent catheterisation is started or by suprapubic catheterization the patient's continence will usually improve significantly.

23.1.2.1 The Overactive Bladder

Neurogenic detrusor overactivity, which causes incontinence when the neurogenic contractions occur, will be resolved by dealing with the hyperreflexia using medication, Botulinum toxin or cystoplasty. Medication is the primary choice of treatment. Botulinum toxin is used when medication fails to lower bladder pressures and abolish hyperreflexia. Cystoplasty is an excellent long-term solution but has become less commonly performed due to the predominance of Botulinum toxin.

23.1.2.2 Sphincter Weakness

For the patient who has sphincter weakness incontinence, which is generally those patients with lower motor neuron lesions in association with acontractile bladders, the treatment is very much directed according to gender and mobility and the patient's needs and desires.

The Female

Tapes, Slings and Colposuspension

For a female patient with sphincter weakness incontinence whether doing intermittent self catheterisation or with a suprapubic catheter a standard female continence procedure can be adopted.

We have experience of using tension free tapes both by the standard TVT and by the TVTO routes with excellent results [5, 6]. However in the light of the current debate regarding the insertion of a tape, other options should be offered to our patients.

It is important not to pull the tape too tight to avoid erosion. However a trans vaginal tape can be an excellent way of resolving incontinence particularly in a patient who is over 40 years of age and can do intermittent self catheterisation.

If there is a significant hypermobility in a younger patient particularly those who have had children a colposuspension procedure is also an excellent way of resolving stress urinary incontinence in a patient with a neuropathic bladder. For the younger patient an autologous sling can be effectively used to correct urinary incontinence and these can be pulled snug such that the patient's continence is protected and yet catheterisation still possible [7]. Artificial urinary sphincters in female patients with neuropathic bladders, who are doing

intermittent self catheterisation can be used but with decreased risk of AUS survival [8].

Bulking Agents

Bulking agents do have a place in the less fit patient particularly patients with long term catheters and can provide continence when other forms of surgery are either not appropriate or deemed difficult because of pelvic fracture injuries. However the results are not often well sustained and the emerging evidence appear insufficient to guide practice [9].

The Male

For the male patient with stress urinary incontinence due to sphincter weakness with neuropathic bladder dysfunction the most effective treatment is with an artificial urinary sphincter. Although bulking agents can be used and we have experience of this the results are not particularly encouraging [10] with approximately 33% of patients rendered continent. However, it can be argued that this is a relatively simple treatment performed as a day case without any long term complications and should not be ruled out. It could be offered to patients who do not wish to have an artificial sphincter.

The artificial sphincter however remains the gold standard for patients with neuropathic outlet weakness. For the patient who has a spinal cord injury who is unable to walk who is sitting most of the day the sphincter cuff should be placed around the bladder neck by abdominal surgery. This is a more technically challenging procedure and rests in the hands of those with a significant experience in this field.

For the ambulant patient with a neuropathic bladder the cuff can be placed around the bulbar urethra. Patients with spinal cord injury who are immobile can have bulbar cuffs placed but they do have a tendency to a greater risk of complications [11].

It has to be accepted that those patients who have sphincter weakness incontinence who are distressed by its presence should be counseled about the risks and complications of an artificial urinary sphincter. The fact that the sphincter will not last for a life time is also important particularly as a patient should be aware of the fact that the sphincter will need replacement at some point over the years. The average life expectancy of the sphincter is in the region of 10 years [12]. Thus for the younger male patient who may need 3–4 sphincters over a life time could expect after 30–40 years to have their management changed possibly to an alternative form of bladder drainage if the sphincter failed or could not be replaced for technical reasons.

Any patient who has had stress incontinence surgery should be on a long term follow up arrangement so that any issues with continence can be dealt with. For a patient who perhaps has had a colposuspension or tape and still has residual incontinence bulking injections may be beneficial.

23.1.2.3 Clam Augmentation Ileocystoplasty

If neurogenic detrusor overactivity cannot be controlled by medication or intravesical Botulinum toxin then an augmentation ileocystoplasty is an excellent surgical option. Although it is a major surgery there is no reason why this procedure should not be offered to patients sooner rather than later. There is no point continuing with recurrent Botulinum toxin injections on a frequent basis if the treatment does not work when a cystoplasty will resolve the problems for the long term. An excellent result can be seen from an augmentation ileocystoplasty in the neuropathic group [13]. Continence procedures can be combined with cystoplasty when indicated [14]. Where catheterization difficulties are encountered prior to a cystoplasty (without or without a continence procedure) a Mitrofanoff procedure should also be considered [15]. Occasionally bladder neck closure may be necessary and thus continent diversion will be necessary if the patient wishes to be continent without having to undergo a surface urinary diversion.

In the future it is likely that some of these procedures will be conducted more minimally invasively using laparoscopic or robotic surgery. The open surgical procedure still is an excellent operation performed through a Pfannenstiel incision and the patient's recovery is relatively rapid. The time of the effectiveness of an augmentation ileocystoplasty is usually 3 months to gain significant benefits. In the neuropathic patient group intermittent catheterisation will be necessary to drain the bladder. Thus provided the patient is able to perform intermittent catheterisation an augmentation ileocystoplasty is an excellent method of treatment of patients with neurogenic detrusor overactivity and should be introduced sooner rather than later in many patients particularly whilst they are younger and fitter.

23.1.2.4 Long-Term Follow-Up

The long term follow up of a patient with a neuropathic bladder having had a cystoplasty would be according to standard rules using annual follow up with an ultrasound scan of the urinary tract and occasional urodynamic studies to make sure the bladder is storing under low pressure.

23.1.3 Restoration of (Parts of) the LUT Function

Sacral root stimulation can offer the ability of voluntary bladder evacuation, and is one of procedures for restoration of (parts of) the LUT function. The anterior sacral root stimulation introduced by Prof Brindley in the 70s has had a place in management of patients with neuropathic bladder dysfunction after a spinal cord injury. The necessity is for a complete lesion to ensure that a posterior rhizotomy can be performed to reduce or avoid the neurogenic overactivity

with simulation of the anterior roots. Many patients have benefited long term from this technology. There is however more recent reluctance of patients to undergo such surgery because of the thought of nerve division. Although patients can be offered this they are often reluctant to go through such surgery. However it should not be excluded although it should be located in specialist centres where experience can be gained from the surgical technique and post operative management [16] and long-term follow-up which will allow troubleshooting of issues when they develop.

23.1.4 Improvement of the Patient's Quality of Life

Quality of life is significantly affected in patients who have suffered a major change in following the development of a neuropathic bladder [17] due to a spinal cord injury or disease process. Bladder function, continence and sexual dysfunction become a primary consideration. Thus, providing continence is essential for these patients. It is very important to ask the question to a patient as to how troubled they are by their urinary problems and to ensure appropriate counseling prior to any intervention and then supervised follow up to improve quality of life. There is no doubt that continence for any patient will provide a greater improvement in quality of life.

23.2 Principles for Treatment of NLUTD

The management of patients with a neuropathic bladder rests upon maintaining a near "normal" situation as existed prior to the development of the neurological dysfunction. The principle is "**low pressure bladder storage with complete bladder emptying"**. Long term follow up will be necessary to ensure that deterioration in upper tract function does not occur and quality of life and longevity is maintained.

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Part IX

Non-invasive Conservative Treatment

Assisted Bladder Emptying

24

Jan Krhut

24.1 Bladder Expression (Credé)

Manual expression of urine is one of the oldest methods of bladder evacuation in patients with neurogenic bladder. It entails the application of manual pressure over the lower abdomen by the patient or another person. In most cases, this technique is utilized in individuals with hypocontractile or acontractile detrusor due to nerve disruption under the level of the sacral micturition center (lower motor neuron lesion).

Even though this method seems simple and straightforward, in light of current knowledge, it cannot be considered neither safe nor effective. Using antegrade and retrograde uretrocystographies during bladder expression, Madersbacher has documented that in the majority of cases, the Credé maneuver was associated with significant subvesical obstruction at the level of the striated urethral sphincter [1]. The likely reason for this is, that by applying pressure over the symphysis pubis, the bladder is pushed dorsally and caudally, while the membranous urethra, which is fixed to the symphysis pubis by puborectal ligaments, does not follow this movement. This leads to kinking of the urethra and restriction of the urethral lumen, which could only be overcome with significant pressure. This situation is made worse by the inability of patients with a lower motor neuron lesion to relax the sphincteric unit. High intravesical pressure could lead to serious complications, which include reflux of urine into the upper urinary tract as well as into the ductus deferens in men. In female patients, there is a risk of pelvic organ prolaps. Increased incidence of hemorrhoids was reported in both men and women. It has been reported that 15–20% of spinal cord injury patients use the Credé maneuver for bladder evacuation. The majority of this population includes older patients with a longer time since injury. Many of them list simplicity of the procedure as a reason [2]. Bladder expression could only be recommended in selected cases of hypocontractile detrusor and low urethral pressure. The data defining acceptable maximal intravesical pressure during manual bladder expression are not available. It is necessary to stress that the high intravesical and/or urethral pressure, high postvoid residual, vesicoureteral reflux and recurrent urinary infections should be considered contraindications for the use of this technique [3].

24.2 Voiding by Abdominal Straining (Valsalva Maneuver)

Bladder evacuation using abdominal straining—the Valsalva maneuver—is another method used by some patients with lower motor neuron lesion, who have adequate voluntary control of the abdominal wall and diaphragm. The mechanism leading to bladder evacuation, as well as the limitations and associated risks, are identical to that of the Credé maneuver. A report evaluating a population of 74 spinal cord injury patients, 23 years post injury, assessed the prevalence of urological complications as a result of the use of Credé and Valsalva maneuvers. One third of patients (31.3%) developed urinary stones, 35.1% developed hydronephrosis and 16.2% of cases led to renal failure [4]. The use of Valsalva maneuver should be discouraged unless urodynamics show that the intravesical pressure is within safe limits.

24.3 Triggered Reflex Voiding

Thirty years ago, triggered reflex voiding was the most frequently used method for bladder evacuation in patients with neurogenic bladder. It induces reflex bladder contractions through various external maneuvers such as suprapubic tapping or scratching of the inside of the thighs. The feasibility of this method depends on an intact sacral micturition reflex (bladder—sacral micturition center—bladder). Triggered

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_24

reflex voiding is usually associated with detrusor-sphincter dyssynergia and therefore represents a potentially dangerous method for bladder evacuation. It often causes a pressure increase in the urinary bladder during micturition, with known consequences for the upper and lower urinary tract. Another consequence of detrusor-sphincter dyssynergia, which occurs during reflex voiding, is autonomous dysreflexia. In most cases, reflex voiding also leads to incomplete bladder emptying. Significant post-void residual means a reduction of functional bladder capacity, which subsequently necessitates more frequent bladder emptying.

Triggered voiding should be used in a limited number of carefully selected patients with adequate urodynamic findings. In most cases, this technique is acceptable in older patients with a long history of the disease, who are familiar with the technique, are well adapted to it and have no complications. This recommendation is supported by published findings showing that the mortality risk due to complications of the neurogenic bladder decreases by 50% with every 10 years since the injury [5]. This technique could also be used in quadriplegic patients who are unable to perform self-catheterization or in whom regular bladder emptying using clean intermittent catheterization by other person cannot be guaranteed. In cases of unacceptably high bladder pressures during voiding, external sphincterotomy should be considered. A routine follow up is absolutely necessary in all patients.

24.4 Behavioral Modification Techniques

According to the current recommendation of the International Continence Society (ICS), behavioral modifications are considered a first-line treatment in all patients with urinary incontinence. Behavioral treatment is simple, non-invasive, inexpensive, and has no side effects. It could be safely used even in patients with severe co-morbidities and could be combined with other treatment modalities. The patients' motivation and compliance are a prerequisite.

24.4.1 Lifestyle Changes

Lifestyle changes are largely based on empirical and observational evidence. The following rules should be followed, especially in patients with predominant symptoms of detrusor overactivity.

- Dietary restrictions: avoidance of spicy food, citrus fruits, carbonated drinks, artificial sweeteners (aspartame).
- Restriction of caffeinated drinks.
- Optimization of fluid intake. Daily fluid intake should be between 1.5 and 2.2 L. Concentrated urine due to low diuresis could cause local irritation of the urothelium. Polyuria due to high fluid intake necessitates increased frequency of bladder emptying. In the case of bothersome nocturia the fluid intake during the last 3 h before bedtime should be restricted.
- Management of adequate bowel emptying through sufficient intake of dietary fiber, use of natural laxatives.

In patients with stress urinary incontinence maintenance of optimal body weight is recommended. It has been documented that 5–10% of weight loss in overweight and obese patients significantly improves continence [6].

24.5 Pelvic Floor Muscle Exercises

Pelvic floor muscle exercises (PFME) were described for the first time in 1951 by an American gynecologist, Arnold Kegel [7]. This treatment modality has since became a broadly used method for conservative management of stress urinary incontinence in females. Originally, this method consisted of several strong and short lasting contractions of the pelvic floor. Contraction of the appropriate muscles has been controlled using vaginal palpation. The goal of this exercise used to be to increase pelvic floor muscle strength, leading to the improvement of passive outlet resistance. This concept was updated in the 80s. Currently, the aim of pelvic floor muscle training is to use the pelvic floor muscle contraction to control the continence according the principle, "find and use" [8].

PFME was traditionally used for treatment of incontinence due to weak sphincter function. But it was proven that it also has a role in the treatment of bladder hyperactivity. This is based on following hypotheses:

1. Barrington theory: According to this theory, urine distending the proximal urethra during initiation of micturition leads to an augmentation of the detrusor contraction. This hypothesis, originally formulated by Barrington, was confirmed in animal experiments by Jung et al., who documented detrusor contraction in response to the stimulation of the proximal urethra [9]. This system of positive feedback improves bladder emptying of healthy individuals, however, it also has its disadvantages. For example, in females with weak pelvic floor muscles, the funneling of the bladder neck and proximal urethra triggers a micturition reflex, causing urgency. Voluntary contraction of the pelvic floor muscles can maintain the closure of the proximal urethra, thereby inhibiting the micturition reflex. This phenomenon has been confirmed in the clinical setting using perineal ultrasonography [10].
2. Shafik theory: This hypothesis is based on the co-innervation of the bladder neck and bladder wall by adrenergic nerves. Stimulation of alpha-adrenergic receptors in

the bladder neck area causes contraction, while stimulation of beta-adrenergic receptors in the bladder wall leads to muscle relaxation. Therefore, stimulation of the proximal urethra by the contraction of pelvic floor muscles leads to simultaneous bladder wall relaxation [11].

3. Recently published studies using functional magnetic resonance have documented that the contraction of the pelvic floor muscles leads to the activation of several brain areas such as medial surface of the frontal lobe, supplementary motor area, cerebellum and basal ganglia, which are engaged during the inhibition of the micturition [12, 13].

PFME could be beneficial in a select group of patients with neurogenic bladder, who have incontinence due to weak sphincter function as well as in those with detrusor hyperactivity [14]. Training of PFME must be supervised by a specialized physiotherapist, experienced in the field of neurourology. It is crucial that the degree of neurological deficit is adequately assessed and treatment is administered accordingly. The patients' ability to voluntarily control the pelvic floor and deep stabilization system has to be assessed as well. In patients who lost their ability to control pelvic floor muscles, the first step of treatment should be to train targeted and isolated voluntary contraction of the pelvic floor, ideally with the help of electrostimulation. This contraction has to be performed independent of breathing. Only after the patient becomes skilled in these two steps, could he or she be instructed to begin using these maneuvers during urgency or in situations associated with increased intraabdominal pressure (i.e. coughing, bending forward, etc.).

PFME has to be considered a part of a comprehensive therapeutic armamentarium. The most profound evidence of its successful use has been documented in MS patients, however this treatment modality could also be used in patients with suprapontine lesions, Parkinson's disease and others [15].

24.5.1 Toilet Training and Bladder Training ("Bladder Drill")

Suprapontine lesions are often associated with a decrease or loss of cortical control of the micturition reflex. The clinical consequence is urge incontinence as a result of terminal detrusor overactivity. The management of these patients should include active micturition training or passive toilet training.

Active micturition training entails a gradual increase in intermicturition intervals based on voiding diary analysis. It requires active participation of the patient. As a first step, fixed intervals between voiding are set based on data obtained using a voiding diary. If the average intermicturition interval is more than 60 min, the voiding frequency is set at an hour. If the time between voids is less than 60 min, the voiding interval is set at 30 min. The patient is instructed to keep regular voiding intervals and empty the bladder even if he or she does not feel the desire to void. These intervals have to be maintained during the daytime. If less than 25% of intervals are associated with incontinence episodes, the interval is gradually increased by 30 min. Most authors recommend 4–12 weeks of training; however, if no effect is evident within 3 weeks, the treatment should be terminated. According to randomized studies performed in non-neurogenic patients, the success rate of this protocol after 6 weeks of therapy is 57% [16]. Reported experiences using this method in neurogenic patients were described in cases of MS patients and patients suffering from ischemic stroke [17].

Passive toilet training entails prompted voiding and timed voiding. The main difference between prompted and timed voiding is, that with prompted voiding the individual has to be brought to the toilet by caregivers, with timed voiding he is still able to go to the toilet on command/verbal prompts. Usually the patient is brought/prompted to the toilet every 2 h. If the interval is based on the voiding diary, the term 'habit training' is used instead.

The principle of passive toilet training is to bring the patient to the toilet prior to experiencing the desire to void. The goal is to eliminate or reduce the number of incontinence episodes. This method is dependent on care providers and does not require active participation of the patient. It is effective in the short-term treatment of daytime urinary incontinence in nursing home residents and home-care clients, if caregivers comply with the protocol. Timed voiding should not be used in persons who are unable to state their name or need the assistance of more than one person to transfer. It should not be continued if, after three day trial, the reduction of incontinence is less than a 20% or if the patient empties his or her bladder successfully less than two-thirds of the time.

24.6 Biofeedback

Biofeedback is a method that allows a patient to improve overall regulation of bodily functions, based on gaining detailed objective information on the very function(s) in need of improved control. Emerging electronic methods allow for collection, processing, and amplification of data regarding biological processes in the human body, which could subsequently be transformed and organized in a manner that is understandable and easy to use by the patient (visual, acoustic or tactile). The most commonly used method in the treatment of patients suffering from both stress and urge urinary incontinence is electromyography biofeedback for PFME. Surface adhesive electrodes attached adjacent to the mucocutaneous anal line bilaterally are most

commonly used. The obtained signal facilitates the process of training selective contraction of the pelvic floor muscles. Data supporting the efficacy of this method in patients with supraspinal lesions and MS have been published [18]. Biofeedback must be considered an integral part of the comprehensive, conservative treatment of patients with neurogenic LUTS.

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Lower Urinary Tract Rehabilitation

25

Marianne de Sèze and Alexia Even

25.1 Introduction

Electrical stimulation (ES) has been tried for many years in different form of neurogenic lower urinary tract dysfunction, aiming to restore emptying and storage function.

Numerous methods have been used, interesting sacral roots as peripheral nerve and pelvic organs, with variable therapeutic success. Some of them are not valuable today, due to their poor feasibility or efficiency.

A major problem to define the place of ES in the neurogenic bladder therapeutic algorithm is the relative lack of randomized controlled study. This methodological restriction lead to limitation for the determination of the true efficacy of varying ES modalities, and their acceptance by health insurance authorities.

Subsequency, in the recent report of the International Consultation of Incontinence, ES was claimed to have an insufficient evidence base depending on the limited number of positive RCTs.

However, some ES modalities such as sacral neuromodulation, tibial posterior and pudendal nerve stimulation have been successful for treatment of neurogenic detrusor dysfunction in the short/middle term, and are worth considering. Their place in the management strategy need to be more defined in the future.

The principles of action, methods and respective interest of the main procedures of ES will be discussed in this chapter.

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25.2 Peripheral Acute Temporary Electrostimulation

25.2.1 External Temporary Electrical Stimulation

25.2.1.1 Penile/Clitoridal

Penile and clitoridal ES activates the motor fibers to the pelvic floor and the intramural uretral sphincter, either directly or by reflex mechanisms, or both [1]. Stimulation of these sites evoked reflexes with the afferent limb in the pudendal nerve inducing concomitant central actions. Three central actions have been described, activation of hypogastric inhibitory fibers to the bladder, central inhibition of the pelvic outflow to the bladder and central inhibition of the ascending afferent pathway from the bladder [1].

ES of pudendal nerve afferents has shown to be an effective method to suppress involuntary detrusor contractions in patients with neurogenic detrusor overactivity (NDO) [2]. Continuous, conditional and semi-conditional stimulation of dorsal penile-clitoridal nerve using cutaneous electrodes has been shown to inhibit bladder contractions. The continuous method applies ES throughout bladder filling whereas the conditional method initiates ES as intravesical pressure begins to rise at the beginning of NDO. The semi conditional ES starts with the first bladder contraction and continuous in cyclic pattern with a preset on-off duration of burst of electric current.

All of these methods take place in an institutional setting, and each has been equally effective to inhibit NDO and increase bladder volume during cystomanometry [3–6].

If the urodynamic effect seems validated, the usefulness of those devices in the daily life, outside the institutional setting, is poor investigated and their feasibility could appear criticable.

Furthermore, in neurogenic patient, the absence of a clinically applicable indicator of the bladder contractions has

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_25

limited the evolution of the conditional DGN stimulation to a fully implantable prothesis. However, in some neurogenic patients with preserved bladder sensation, subject controlled DGN stimulation may have an interest.

In this way, a recent report, based on 11 neurogenic patients with NDO, underwent a 5-day study at home with dorsal genital nerve stimulation, underlined the feasibility and the globally positive outcomes of the study [5]. In this study, stimulation was provided with surface electrodes placed by the patients either on the dorsal penile shaft in males and on or close to the clitoris in women. The electrical stimulator was manually activated by pressing a button. Patients were asked to press the button as soon as they felt the need to pass urine. The stimulation was remained on for 30 s, after which it automatically switched off. The first and 5 day were with no stimulation whereas 2–4 were with stimulation. Evaluation was made by urodynamics at the beginning and at the end of the study and with bladder diary. A significant benefit was shown on bladder capacities and mean volume per day voided [5]. Nevertheless, this study has some limitations, namely including the small population, the short term period of stimulation and evaluation and the lack of control group.

The efficacy and feasibility of this technique warrants further investigation in a larger controlled study. Furthermore, there are challenges of chronic clinical deployment at this location.

To date, the stimulation of penile or clitoridal regions in neurogenic patient cannot be considered a socially-relevant and non invasive method and it should be used with great caution.

25.2.1.2 Intracavital: Vaginal or Rectal

The putative therapeutic effect of non-surgically implanted vaginal electrodes results from reflex response of the stimulation of the afferent fibers of pudendal nerve.

Anal stimulation inhibits the bladder in a similar fashion by a reflex with its afferent limb in pelvic nerve branches to the anal region.

The method implies the insertion of plugs equipped with electrodes into the anal canal and/or the vagina.

For acute or short term stimulation, the patient is treated in a limited number of session taking 15/20 min each, and the used intensity is as high as possible, i.e. just below the level of discomfort.

Vaginal devices have been proposed for the treatment of urinary stress incontinence and detrusor overactivity [7].

The anal plug was applied for the treatment of urinary incontinence.

If the interest of intracavital ES has been reported in non neurogenic patients suffering from overactive bladder or mixte incontinence, the results in neurogenic patients are disappointing [8, 9].

The interest of anal ES for treating urinary incontinence and NDO has been reported by Kajbafzadeh et al., in children with myelomeningocele. Thirty children were enrolled in this sham controlled study, and then randomly allocated to treatment (anal transcutaneous ES) or control (sham stimulation) groups. ES or sham were done during 20 min, three times a week for 6 weeks. Urodynamics and clinical symptoms were evaluated before and after ES and 6 months later. Significant improvement was shown on all urodynamics parameters (detrusor pressure, bladder capacity, compliance, detrusor sphincter dyssynergia and post void residual) at the end of ES in the treatment group compared to pretreatment measure and sham group. Continence was achieved in 78% of the children after ES and 60% had persistent continence for 6 months. Urinary frequency and enuresis also significantly improved in the treatment group [8].

On the other hand, Previnaire et al. were not able to demonstrate the efficacy of anal ES combined with DGN ES in five spinal cord injured patients: neither the cystometric bladder capacity nor the micturition charts had significantly changed after a five times a week 4 week study [10].

Poor outcome was also reported by Primus et al. in MS women suffering from NDO [9, 11]. In these studies, 30 women were treated with an intravaginal electrode during 3 weeks, with 15 sessions of 20 min. The urodynamic effect and subjective improvement were poor, and relapse occurred within about 2 months. To retain improvement, MS patients do need daily home stimulation treatment [9, 11].

Finally, in neurologic patient, the use of these types of stimulator is limited and there is no evidence based data to support their efficiency. In addition, there were no data concerning the long term effectiveness of those ES device in neurogenic patients In addition, the cost-benefit analysis is weak.

25.3 Peripheral Chronic Pudendal Stimulation

Here chronic stimulation is defined as a period of at least 2 weeks. Afferent pudendal nerve stimulation has demonstrated to inhibit the micturition reflex, abolish uninhibited detrusor contractions and increase bladder capacity in animals and humans [12].

The fibers of the pudendal nerve are composed mainly of afferent sensory fibers from S1, S2 and S3, with inter-individual variations. Some of the patients seem to have a preferential S2 distribution, which could explain some of the failures of S3 neuromodulation. These patients could benefit from directly stimulating the pudendal fibers in order to improve voiding dysfunction.

Unlike stimulation of the dorsal genital nerve, stimulation of the pudendal nerve requires the implantation of an electrode. According to the anatomy, electrical stimulation of the

pudendal nerve is possible at several locations along their course from the sacral nerves to the penis or clitoris. Pudendal nerve can be accessed for stimulation: at ischial spine, by posterior or perineum approach or at Alcock's canal.

Two types of devices can be implanted for pudendal nerve stimulation: the Bion® system and tined leads InterStim®, commonly used for sacral neuromodulation.

The Bion® microstimulator was developed to overcome the need to tunnel leads from a central controller. It contains an implantable electrical stimulator that requires no lead, with a lithium rechargeable battery. It may be implanted adjacent to the pudendal nerve at Alcock's canal via the perineum under scanography. All implanted patients are given a remote control and a charging system (15–30 min per day by seated station on a specially chair pad). It is designed to provide stimulation of the pudendal nerve while avoiding the complications of a leaded system, as lead migration [13].

The chronic pudendal nerve stimulation via the Bion® stimulator has been proposed for the treatment of idiopathic detrusor overactivity, after failure of drug treatment, pelvic floor therapy and various forms of neuromodulation. Two pilot studies [14] have demonstrated a clinically significant response after implantation in patients with a positive response to the acute test. On average, the number of incontinence episodes per day, the number of pads used per day and the leakage severity index had decreased after 6 months, on the other hand, there were no significant changes in cystometric studies. Vaginal dryness, altered bowel function and mechanical irritation during bicycle riding were mentioned as device related side effects [14].

The efficacy of the tined lead InterStim® pudendal stimulation, placed under neurophysiological guidance, has been evaluated in the literature in neurological and non-neurological populations.

Spinelli et al. implanted 15 patients, with neurogenic overactive bladder after drug and sacral neuromodulation failure for three of them. He showed a decrease of incontinent episodes per day and a significant improvement in the maximum cystometric capacity; but no significant decrease of the maximum pressure, which is one of the risk factor for uro-nephrologic complications in this population. Patients used three different stimulation modes: on demand at appearance of urge obtaining continence and increase time to go to the toilet, only during the day, or continuous stimulation. The interest of semi conditional stimulation could be to save the battery life compared to continuous stimulation [15].

Peters et al. have shown interesting results with pudendal neuromodulation on frequency, average voided volume, incontinent episodes and urgency in 84 patients, including 44 patients who failed neuromodulation. But the interpretation of this study is limited by the heterogeneity of the population, with various urologic diseases. However it is interesting to note that the majority of subjects, who did not respond to sacral stimulation, did respond to pudendal stimulation [16].

In order to define the place of pudendal neuromodulation compared to sacral neuromodulation, Peters et al. conducted two single blinded, randomized and crossover trials in interstitial cystitis and voiding dysfunction (urinary urgency/frequency, urge incontinence or urinary retention).

Among patients with voiding dysfunction responding to neuromodulation (symptoms improved more than 50% during test period), 79% desired to have PN implantation compared to 21% for SNS. The pudendal lead showed a greater overall symptom improvement than the sacral lead and a greater subjective improvement for pelvic pain, urinary frequency, urgency and bowel movements [17].

In the same way, most of patients with interstitial cystitis (13 of 17) chose the pudendal lead for the final implant. PNS was better than SNS for urgency and frequency on a 7 point scale. On the other hand, no significant differences for pelvic pain, bowel function, vaginal pain or incontinence were demonstrated [18].

Concerning, bowel function, results are discordant, but in these studies, anorectal function was not studied as a primary criterion.

To the extent that few studies have been carried out on pudendal nerve stimulation, sacral neurostimulation remains the primary therapy, in case of drug failure for neurogenic or idiopathic overactive bladder. But it is interesting to note that some patients respond positively to pudendal nerve stimulation, whereas they had poor results with sacral neuromodulation. The current use of pudendal nerve stimulation is also limited by the lack of specific device commercially available.

25.4 Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex could induce a long lasting modulation of spinal cord excitability [19]. Such stimulation could produce long term potentiation or depression of neuronal circuits. Low frequency rTMS tends to effect a reduction in cortical excitability, whereas higher frequencies increase excitability of the corticospinal pathway and reduces cortical inhibition.

rTMS has been proposed in the treatment of urinary disturbances (increased frequency, urgency and urge incontinence) in patients with Parkinson's disease [20]. In this study involving eight patients, repeated low frequency transcranial magnetic stimulation for 2 weeks over the motor cortex (five sessions/week) allowed a significant improvement of the first sensation volume and bladder capacity at urodynamic evaluation 1 week after stopping the stimulation. Clinical assessment of irritative symptoms by IPSS scores showed immediate and persistent improvement at 2 weeks, but not at 4 weeks.

A study in 10 multiple sclerosis patients revealed an improvement after 2 weeks of high frequency transcranial

magnetic stimulation (5 days/week), in patients with detrusor underactivity at urodynamics: significant reduction of post void residual and significant increase of Pdet@Qmax, with a subjective improvement of urinary dysfunction. No significant changes were found in patients with detrusor overactivity and detrusor-sphincter dyssynergia [21].

These two studies tend to show that the effects on urinary disorders can be very different according to the stimulation parameters (high or low frequency).

In spinal cord injured patients, one of the main problems of application of rTMS is that high motor thresholds are unacceptable levels of stimulation. Individual variation in the extent and the level of SCI and the consequent variability in impact on sensorymotor control also create difficulty in formulating plasticity inducing rTMS protocols [22].

25.5 Electrical Stimulation Combined with Pelvic Floor Muscle Training: Biofeedback

Pelvic Floor Muscle (PFM) electrical stimulation techniques have been used for both stress incontinence and detrusor overactivity in neurogenic patients. The procedure implicate an electrical impulse generator applied via the vagina, anus, penis, clitoris or perineal body.

PFMES could be considered for initiating a contraction and increasing cortical awareness of the PFM when there is an intact neural pathway but an inability to perform voluntary contraction. The technique aims to have the patients 'joining in' with the electrically induced contractions to gain increased cortical awareness and control, and once achieved, to use active exercise.

PFMES could also be considered for assisting in normalizing reflex activity for bladder inhibition.

It is thought that the resulting reflex pelvic floor contraction has the same inhibitory effect on detrusor activity as does a voluntary contraction of PFM. Both PFM training and suppression techniques will require intact neural pathways.

Some parameters have been suggested for PFM intracavital stimulation [23]: It is usually considered that a frequency of 35–40 Hz and a pulse duration of 0.25 ms, at intensity sufficient to provoke a PFM contraction is valuable for stress incontinence.

For detrusor inhibition, suggested parameters are frequency of 5/10 Hz, pulse duration of 0.5/1 ms at maximum current tolerated intensity, with continuous or short rest periods every 10 s. Of course, if the parameters used should be in line with current evidence, they should be appropriate for the individual [23].

The interest of PFM training in neurogenic patient was mainly reported in multiple sclerosis patient suffering from detrusor overactivity. De ridder et al. showed that it was useful for decreasing frequency, daily incontinence episodes and increasing mean functional bladder capacity in MS patients with low disability score and without pelvic floor spasticity [24]. Beneficial effect was also reported by Mc Clurg in MS patients presenting LUT dysfunction [25]. In neurogenic patient suffering from MS, some report suggest that the addition of neuromuscular electrical stimulation to a program of PFM training and EMG biofeedback had superior outcomes [26].

Biofeedback (BFB) for pelvic floor therapy usually utilizes auditory or visual feedback to enhance a person's knowledge of a particular muscle's activity.

Some open studies reported the beneficial effect of BFB in neurogenic patients, namely multiple sclerosis [26].

One RCT was found that compared the effect of a combination of six sessions of initial ES, followed up with BFB and PFM training, with no treatment. Fifty women and 30 men with multiple sclerosis participated in the 6-month treatment program. The results demonstrated a significant improvement in urgency, incontinence episodes, and nocturia in the treatment group. Improvement in the subjective severity of urinary symptoms was only significant for men. At 6 months, the treatment group reported less handicap than the control group in traveling, social shame and need for diapers [27].

One RCT compared the efficacy of PFM versus transcutaneous posterior nerve stimulation (TPNS) in 31 adults MS patients with mid disability [28]. Patients were randomized to receive 9 sessions of 30 min weekly of PFM (muscle endurance and relaxation) or TPNS (rectangular alternative biphasic current with low frequency). Evaluation was done before and at the end of the treatment by quality of life and Urinary Symptoms Profile score of frequency and urgency episodes. Both treatments were significantly effective in the same way for improving symptoms related to urgency [28].

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Repetitive Magnetic Stimulation

26

Somrot Phonglamai and Sintip Pattanakuhar

26.1 Introduction

Magnetic stimulation is a non-invasive method using magnetic energy to modulate the function of nervous system. The stimulation can apply over the brain, spinal cord, nerve roots or peripheral nerve and muscle. Focusing on the stimulation over the brain, namely transcranial magnetic stimulation (TMS), the first report of using this application in humans was published in the Lancet in 1985. Barker succeeded in using TMS for painless recording of motor evoked potential (MEP) from the hand and finger muscles [1]. To date, TMS is approved by the US Food and Drug Administration (FDA) in treatment-resistant major depressive disorder (2008), pain associated with certain migraine headaches (2013) and obsessive-compulsive disorder (2018). TMS is also used in many researches for treating neuromuscular conditions including neurogenic bladder.

26.2 Principles

26.2.1 Components

TMS consists of the main unit and a stimulation coil (Fig. 26.1). The stimulation parameters (e.g., frequency, intensity, train duration, intertrain interval time) are set on the main unit, and TMS is conducted by applying the stimulation coil to the surface of the skull or other stimulation sites.

26.2.2 Frequencies

Four types of frequencies were introduced clinical application: single pulse, paired-pulse, repetitive stimulation and theta burst stimulation (Fig. 26.2). Single pulse is one-pulse stimulation while paired-pulse is stimulation with two distinct stimuli through the same coil at a range of different intervals. Both types are used to explore brain function. Repetitive stimulation is groups of pulses with a regular interval which commonly used to induce changes in brain activity that can last beyond the stimulation period. The 5 Hz or higher frequency of repetitive stimulation is called high-frequency (HF) repetitive stimulation, while the 1 Hz or lower frequency is called low-frequency (LF) repetitive stimulation. The HF repetitive stimulation enhances local neural activity at the stimulated site, but the low one has suppressive effects. Another stimulation technique is theta burst stimulation (TBS). This stimulation consists of a burst of three pulses at 50 Hz, repeated every 200 ms. Interestingly, this high-frequency protocols can either increase or decrease activity in motor cortical circuits. There are two types of TBS, continuous TBS (cTBS) that produces an inhibitory effect and intermittent TBS (iTBS) that produces an excitability effect [2].

26.2.3 Sites of Stimulation

Magnetic stimulation can be applied over the brain, spinal cord or peripheral nerves depend on the conditions. When

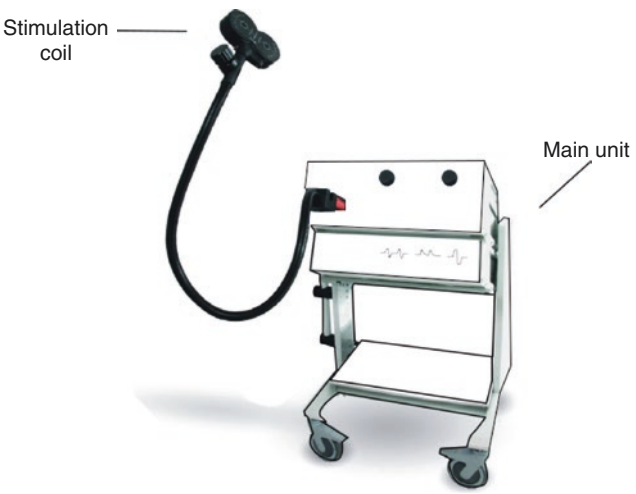

Fig. 26.1 Magnetic stimulation device

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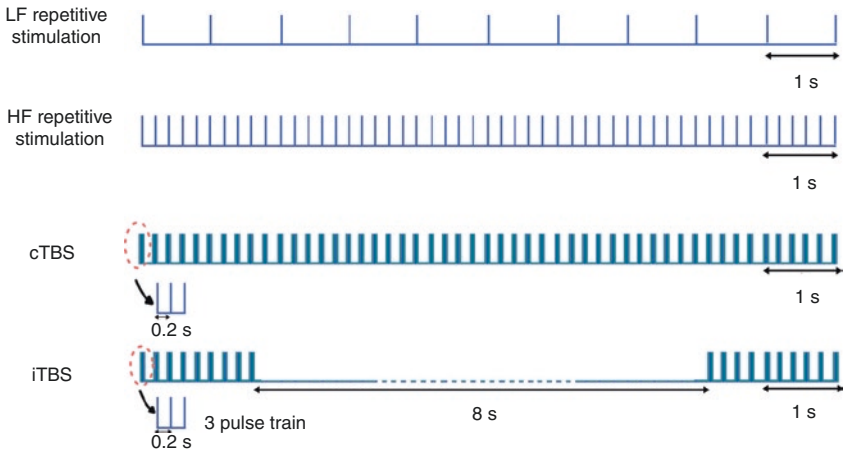

Fig. 26.2 Sample of magnetic stimulation frequency

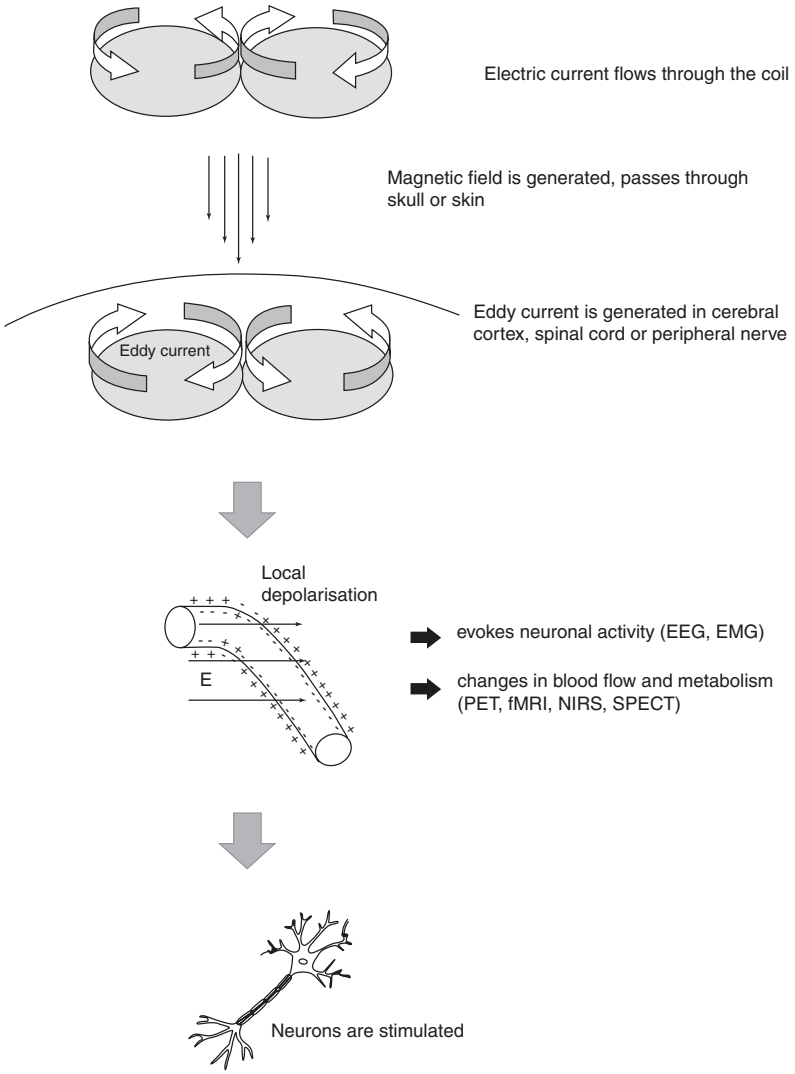

Fig. 26.3 Mechanism through which TMS stimulates the cerebral cortex, spinal cord or peripheral nerve. (Adapted from Abo 2005 [3])

the magnetic stimulation are applied over the brain, it is called transcranial magnetic stimulation (TMS), and over peripheral nerves, it is called peripheral magnetic stimulation (PMS).

26.2.4 Mechanisms

The stimulation is based on the Faraday's law on electromagnetic induction. As shown in Fig. 26.3, when an electric

current flows within a circular coil, a magnetic field is generated perpendicular to the plane of the coil and reaches the cerebral cortex, spinal cord or peripheral nerve after passing through skin, soft tissues, skull or bone. The electric current flowing through the coil is not a steady-state current but constantly changes its velocity [3].

Focusing on the mechanism acting at central nervous system of magnetic stimulation, evidence has shown that the effects of repetitive TMS (rTMS) depend on the activity in *N*-methyl-D-aspartate receptors [4], resembling mechanisms involved in an increase in synaptic efficiency is called long-term potentiation (LTP). LTP is the patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons. A decrease in synaptic efficiency is called long-term depression (LTD). LTD is an activity-dependent reduction in the efficacy of neuronal synapses longer following a long patterned stimuli. The effects of rTMS on the local excitability of the cerebral cortex are alterations in synaptic efficiency, which are the basis of brain plasticity, the ability to reorganize itself by forming new neural connections throughout life to compensate for injury and disease. According to the results of animal studies, the alteration in synaptic efficiency by rTMS appeared to be mediated by changing neurotransmitters. While the activation of the glutamate system enhanced brain plasticity, the activation of the Gamma-aminobutyric acid (GABA) system decreased brain plasticity [5–7]. These mechanisms were also applied to spinal cord injury recovery which called spinal cord plasticity.

One important concept among world-wide magnetic stimulation experts, magnetic stimulation should not be the only one single treatment for any condition. Magnetic stimulation alters synaptic efficiency including LTP and LTD induction, promotes collateral sprouting, axonal regeneration, remyelination, reverse of conduction block and neurogenesis to facilitate the natural functional reorganization, and these effects might enhance long-term and permanent structural reorganization when combining with other rehabilitation modalities, such as physical therapy or occupational therapy (Fig. 26.4) [3].

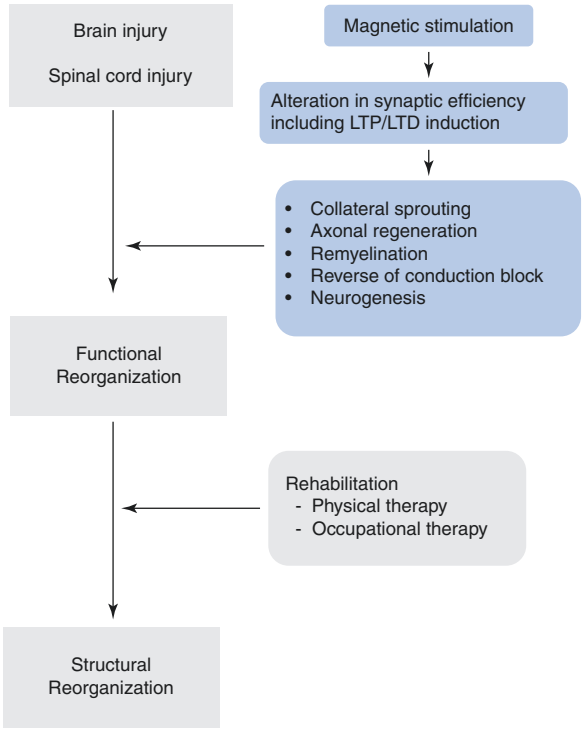

Fig. 26.4 Functional and structural reorganization in the restoration of neuronal function. (Adapted from Abo 2005 [3])

26.2.5 Adverse Effects

The most commonly reported side effect of TMS is headache and neck pain, which has been reported around 20–40%. It is largely believed to occur due to muscle tension, generated either by the stimulation itself or the posture during the long process of stimulation.

Acoustic trauma via TMS coil that produces a deceptive loud clicking noise (120–140 dB). In order to prevent this adverse effect, subjects and operators are recommended to wear earplugs during the full duration of treatment.

Syncope or fainting can occur by several reasons such as hypoglycemia, dehydration, anxiety, physical discomfort or psychological discomfort.

Seizure can be theoretically induced during two different periods of stimulation: (1) during or immediately after rTMS and (2) post-stimulation due to the modulation of cortical excitability. The seizure is usually transient, less than 5 min, and no serious complication.

26.2.6 Contraindications

The absolute contraindication is the stimulation over the implanted cranial electrodes or cochlear implants. TMS may cause heating or induce voltages within ferromagnetic electrodes or medical devices implanted in the cranium.

The relative contraindications as follows:

- Uncontrolled seizure within 3 months
- Recent drug withdrawal: alcohol, barbiturates, benzodiazepines, meprobamate, and/or chloral hydrate may significantly reduce a subject's seizure threshold.
- Drug interactions: some medicines may lower seizure threshold such as alcohol, amitriptyline, chlorpromazine, clozapine, ganciclovir, imipramine, nortriptyline and theophylline.
- Pregnancy: as the magnetic field generated by TMS decays rapidly with distance, any fetal exposure to TMS effects is unlikely.
- Children: nearly 100 studies reporting TMS application to pediatric populations without serious adverse effects.

It has been cautiously concluded that single and paired-pulse TMS is safe in children above the age of 2 [8]. For children younger than 2 years, data about risk for acoustic injury are not available, and therefore specialized hearing protection may be required [9].

26.3 Neurogenic Bladder

26.3.1 Spinal Cord Injury

Because magnetic stimulation is novel intervention and widely studied mostly in psychiatric and neurologic conditions, study in neurogenic bladder from spinal cord injury (SCI) has also limited. The first investigation of acute effect of magnetic stimulation was performed in seven SCI patients with intractable detrusor hyperreflexia. The provocation tests produced consistent and predictable detrusor hyperreflexia. After that, multi-pulse magnetic stimulation at 20 Hz for 5 s over the sacrum was applied. Maximally evoked toe flexor EMGs provided the landmark for the S2–S4 sacral roots. There was an obvious acute suppression of detrusor hyperreflexia and profound reduction in detrusor contraction (Fig. 26.5) [10].

Another study investigated in 22 SCI subjects stimulating the sacral nerves or the suprapubic region. With sacral stimulation, the mean change in bladder pressure (Pves) was 24.4 ± 4.88 cm H_2O; with suprapubic stimulation, the mean change in Pves was 16.5 ± 4.44 cm H_2O. The change in Pves with sacral stimulation was higher than with suprapubic stimulation. Seventeen subjects demonstrated voiding, either with sacral or suprapubic stimulation. Magnetic stimulation of the bladder has the potential to be a useful non-invasive technology for bladder emptying and bladder training in patients with neurogenic bladders [11].

According to the current study on neurogenic overactive bladder dysfunction (OAB) in 80 spinal cord injured subjects, there was a significant increase in the maximum cystometric capacity, volume at first uninhibited detrusor contraction and maximum urinary flow rate. The study proposed that magnetic stimulation activates efferent nerves and motor endplates of the pelvic floor muscle, which provide better muscle strength and endurance. Moreover, magnetic stimulation affects the somatic nerve firing rate responsible for pelvic muscle and sphincter tone [12].

Focusing on improving sensation of bladder filling by using magnetic stimulation, no study was found. The details of studies are shown in Table 26.1.

The summary of proposed mechanisms was shown in Fig. 26.5. The HF magnetic stimulation at sacral roots stimulate directly the pelvic and pudendal nerve efferents to detrusor and urethral sphincter and thus directly potentiate contractile mechanisms. If the optimal stimulation was reached, sphincter muscle fatigue and voiding can occur. Moreover, the magnetic pulses stimulate the afferent sacral nerve, might induce an interneuronal change in the spinal reflex arc or spinobulbospinal reflex arc to inhibit the activity of the C-fibres that become dominant under conditions of neurological injury and thereby inhibit bladder overactivity.

The HF magnetic stimulation at suprapubic area directly stimulates the abdominal muscles, which in turn compress the bladder and activate afferent fibers from the bladder. The afferent signal reaches the pontine micturition center and subsequently elicits reflex voiding via pelvic nerve, similar to suprapubic tapping.

26.3.2 Lumbosacral Plexopathy

One study evaluated improvement of the urinary incontinence associated with lumbosacral plexopathy by 15 Hz repetitive lumbosacral magnetic stimulation (rLMS) with a total of 1500 pulses/session for 10 sessions at S2 level. The results suggested that rLMS can improve symptoms by decreasing frequency and incontinence of micturition during the day and night for up to 1 month. The mechanism of rLMS

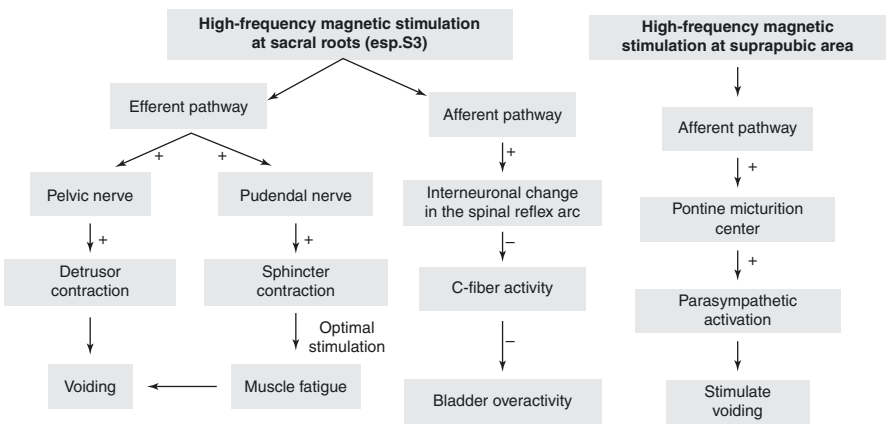

Fig. 26.5 Summary of proposed mechanisms in neurogenic bladder from SCI

Table 26.1 Magnetic stimulation studies in urinary symptoms

References	No. of patients	Treatment	Control	Stimulation frequency, intensity	Pulse/session Number of sessions	Result
Spinal cord injury						
Sheriff et al. 1996 [10]	7	S2–S4 roots	NA	20 Hz	100 pulses 1 session	Acute suppression of detrusor hyperreflexia
Lin et al. 1997 [11]	22	L4 spine midline	Suprapubic area	20 Hz, 50–90%	40 pulses 1 session	Sacral stimulation is more effective than suprapubic stimulation in activating the detrusor muscle
Fergany et al. 2017 [12]	80	Sacral roots	TENS (10 Hz)	15 Hz, 50%	1500 pulses 20 sessions	Magnetic stimulation increases bladder capacity and maximum urinary flow rate more than TENS
LS plexopathy						
Khedr et al. 2011 [13]	26	S2 root	Sham	15 Hz	1500 pulses 10 sessions	Number of voids and incontinence was significantly reduced
Parkinson's disease						
Brusa et al. 2009 [14]	8	Pelvic M1 (1 cm ahead of Cz)	NA	1 Hz, 65%	900 pulses 10 sessions	rTMS increase bladder capacity and first sensation of filling phase
Multiple sclerosis						
Centonze et al. 2007 [15]	10	Leg M1, affected spastic limb predominantly	NA	5 Hz, 100%	1000 pulses 20 sessions	Significant reduction of PVR without change in filling phase
Urinary incontinence						
Galloway et al. 1999 [18]	64 SUI	Magnetic chair	NA	15 Hz for 10 min then 50 Hz for 10 min	12 sessions	Magnetic stimulation reduces leakage episode and number of pad change
Lo et al. 2013 [19]	49 SUI 44 QAB	Magnetic chair	NA	50 Hz for SUI 10 Hz for OAB	20 min 18 sessions	Magnetic stimulation improve symptoms and quality of life in SUI and OAB

Cz primary motor cortex (Brodmann area 4), *M1* motor cortex, *NA* not available, *OAB* overactive bladder syndrome, *PVR* post-void residual urine, *SUI* stress urinary incontinence, *TENS* transcutaneous electrical nerve stimulation

may stimulate directly the pudendal nerve efferent to both external urethral and anal sphincters. Stimulation will also activate directly the peripheral afferent fibers and evoke sensory input to spinal cord. Moreover, rLMS could modulate the excitability of cortico-anal pathways and drive compensatory changes within the cerebral cortex [13].

26.3.3 Parkinson's Disease

The 1 Hz rTMS for 10 days was performed in Parkinson's disease with involuntary detrusor overactivity. The results showed rTMS improves voiding symptoms. However, the duration of the effect, parameters and the appropriate patient selection are still under investigation. rTMS may be induced an opposite modulation of the descending corticospinal tract output targeting the detrusor muscle, resulting in a reduced bladder overactivity (Fig. 26.6) [14].

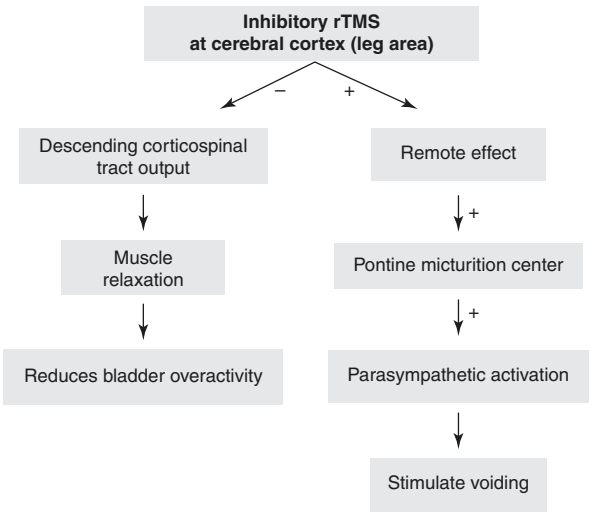

Fig. 26.6 The proposed mechanism of magnetic stimulation for bladder dysfunction in Parkinson's disease

26.3.4 Multiple Sclerosis

Centonze et al. tested the effects of 5-Hz rTMS over the motor cortex in multiple sclerosis (MS) subjects complaining of lower urinary tract symptoms either in the filling or voiding phase. The result showed that motor cortex stimulation with 100% RMT, 5-Hz rTMS once a day, 5 consecutive days over 2 weeks enhances the voiding phase of the micturition cycle, This suggests that the excitability of the enhancing corticospinal tract might be useful to improve detrusor contraction and/or urethral sphincter relaxation in MS patients with bladder dysfunction [15].

26.3.5 Stroke

Urinary incontinence (UI) is common after acute stroke. Evidence showed that 32–79% of patients after stroke experienced UI on admission, reducing to 25–28% at discharge [16]. Similar to the multi-center study showed 45% of patients experienced UI on admission, reducing to 23% at discharge. This means that incontinence occurring after a stroke is usually transient [17]. Therefore, no study of stroke patient with neurogenic bladder and magnetic stimulation was found.

26.3.6 Non-neurogenic Urinary Incontinence

Apart from neurogenic bladder, non-neurogenic urinary incontinence (UI) is one of the common urinary problem among normal population. Magnetic stimulation is a novel tool approved as a conservative treatment for UI by US FDA (Neocontrol system, Neotonus Inc., Marietta, Ga) (Fig. 26.7). In 83 women with stress urinary incontinence (SUI) stimulated with 5 Hz for 10 min then 50 Hz for 10 min, twice a week for 6 weeks showed the number of pads used per day was reduced, the frequency of leak episodes per day was reduced and increased detrusor stability [18].

Moreover, there was significant improvement in stress urinary incontinence (SUI) and overactive bladder syndrome (OAB) in female patients. In SUI group, 50 Hz extracorporeal magnetic stimulation was applied for 20 min. In OAB group, 10 Hz EMS was applied for 20 min. Both groups were performed twice weekly for 9 weeks. There was a significant improvement in both Urogenital Distress Inventory Short Form and the Incontinence Impact Questionnaire Short Form total score in both groups [19].

A systematic review in 2015 showed magnetic stimulation provides short term improvement of UI symptoms in women but no strong evidence to support the long term benefits of using magnetic stimulation in the management of UI [20].

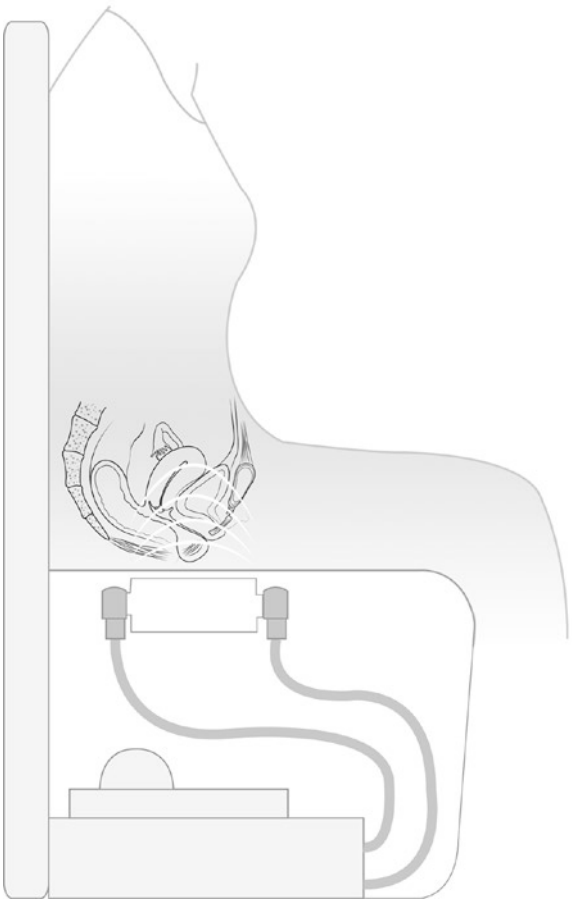

Fig. 26.7 Diagram of the sagittal section of the female pelvis positioned on the seat. The shape of the pulsed electromagnetic fields is shown

26.4 Current Applications and Researchs

26.4.1 Psychiatric Disorders

The US FDA approved for major depressive disorder since 2008. A large amount of evidence supports the conclusion that high-frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS of the right DLPFC exerts an antidepressant effect [21]. The optimal patient for TMS appears to be someone whose depressive episode has lasted 3 years or less; has failed between one and four adequate antidepressant trials (both medication and psychotherapy); and does not have psychotic features [21].

The evidence-based guideline for rTMS application suggested using in anxiety disorder, auditory hallucination, negative symptom of schizophrenia, addiction and craving [21]. To date, these psychiatric disorders are still under investigation for FDA approval.

26.4.2 Cerebrovascular Disease

The review rTMS has been reported to be a safe procedure for clinical rehabilitation of stroke patients. After stimulation, an increase of the lesioned hemisphere's excitability and/or a decrease of the unaffected hemisphere's overactivity is often observed. These changes provide evidence for the role of TMS on restoring the balance between hemispheres' activity. In fact, the patients showed significant improvements in the domains of motor function following rTMS intervention. As acknowledged by several authors, TMS should be combined with conventional rehabilitation because stimulation optimizes the effects of other interventions instead of providing the brain all the changes needed for skill acquisition [22].

In 2015 the study investigated whether 80% MT of 5 Hz iTBS to reduce upper limb spasticity in 15 stroke patients. The result showed that a single session of iTBS over the affected motor cortex caused a transient reduction in spasticity for less than 30 min after stimulation [23].

26.4.3 Parkinson's Disease

The study assessed the different symptom improvements for Parkinson's disease after a combined deep TMS (dTMS) stimulation low-frequency (1 Hz) at primary motor cortex for 15 min and high-frequency (10 Hz) at prefrontal cortex for 15 min, five sessions per week for 3 weeks. The result showed dTMS treatment induced significant improvements in motor and non-motor symptoms, ADL, gait, posture, balance, risk of fall, gait speed, autonomic and depressive symptoms of Parkinson's disease for at least 30 days [24].

26.4.4 Spinal Cord Injury

26.4.4.1 Sensory and Motor Function

Patients with American Spinal Injury Association Impairment Scale (AIS) A, when the examination is performed at 72 h post-injury, 84% of the initial AIS impairment A patients remain as AIS A, 8% converting to AIS B, 5% converting to AIS C and 3% converting to AIS D. When the examination is performed at 30 days post-injury, 95% of the initial AIS A remain as AIS A, 2.5% converting to AIS C and 2.5% converting to AIS D (Table 26.2) [25]. Moreover, in complete SCI patient which neurologically complete by clinical criteria, but electrophysiologic evidence of axonal conduction across the site of injury can be found [26]. Furthermore, a study in anatomical recovery after incomplete spinal cord injury in rats showed spontaneous extensive remodeling, based on axonal sprout formation and removal [27].

Table 26.2 Prediction of recovery according to AIS impairment scale [25]

AIS grade at admission	A	B	C	D
First examination at 72 h	One-year follow-up AIS grade			
A	84%	8%	5%	3%
B	10%	30%	29%	31%
C	2%	2%	25%	67%
D	2%	1%	2%	85%
First examination at 30 days	One-year follow-up AIS grade			
A	95%	0%	2.5%	2.5%
B	0%	53%	21	26%
C	1%	0%	45%	54%
D	2%	0%	0%	96%

Therefore, this information suggested that even in neurological complete SCI, there is some improvement in the nervous system like brain plasticity, as a spinal cord plasticity.

TMS was first used in patients with SCI in the early 1990s. Some studies have examined the effects of rTMS over the motor cortex on sensory and motor function. Three studies evaluated rTMS and sensorimotor recovery.

First, 5 Hz rTMS over M1 hand representation for 5 days in 15 chronic incomplete and complete SCI patients. There was no change in sensory and motor function, assessed by the AIS and neurophysiological assessment by resting motor threshold (RMT), motor evoked potential (MEP) amplitude or duration of cortical silent period [28].

Second, 10 Hz rTMS over M1 hand representation for 5 days in four chronic incomplete SCI patients. Sensory and motor function assessed by AIS were improved. These improvements last for at least 3 weeks [29].

Third, 20 Hz rTMS over M1 leg representation for 15 days in 17 subacute incomplete SCI patients. There were improvement in motor function assessed by the AIS and gait function assessed by 10-m walk test and timed Up & Go test for at least 2 weeks [30].

In summary, the sensory and motor function improvement from functional and neurophysiological assessments are limited and variable, but appear to be present when higher rTMS frequency and intensity were used [31].

26.4.4.2 Spasticity

In human, corticospinal cells exert modulation over a large group of spinal interneurons [32]. Theoretically, it is possible that activating corticospinal neurons by rTMS might induce long-lasting changes in spinal neuronal circuitries. In patients with multiple sclerosis and stroke, the evidences showed that high-frequency rTMS are effective in decreasing spasticity [33].

In patients with incomplete SCI, two studies have reported the effect of rTMS over the leg representation of the M1. High-frequency 20 Hz rTMS applied to M1 leg motor area for 5 days in subacute and chronic incomplete SCI produced

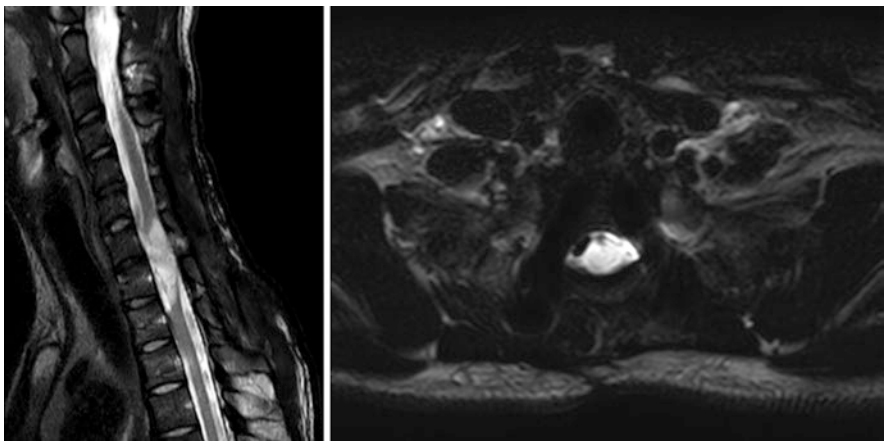

Fig. 26.8 Cervical MRI (October 2017)

significant clinical improvement in lower limb spasticity. The improvement lasted for at least 1 week but was there was no change in corticospinal or segmental reflex excitability [34]. Additionally, when using 20 Hz rTMS for 15 days, spasticity measured by the MAS was significantly reduced, but no neurophysiological testing was conducted [30].

26.4.5 Other Neuromuscular Diseases

In author's clinical practice, magnetic stimulation has significant clinical improvement in other neuromuscular conditions such as traumatic brain injury, cognitive impairment, cerebral palsy, aphasia, peripheral polyneuropathy, diabetic neuropathy, neuropathic pain, carpal tunnel syndrome (sensory and motor involvement), partial nerve entrapment, radiculopathy, neurogenic thoracic outlet syndrome, irritable bowel syndrome, dysmenorrhea, restless leg syndrome and myofascial pain syndrome. But most of the effects are transient and further well-design study should be investigated.

26.5 Case Reports

A 19-year-old man had a motorcycle accident in September 2016. Magnetic resonance imaging performed on the day of injury revealed a C5–C7 fracture, then C4–T3 internal fixation was performed (Fig. 26.8). According to the International Standards for Neurological Classification of Spinal Cord Injury, he had T1 complete paraplegia (AIS class A). Manual muscle test for upper extremities showed grade 5 and lower extremities showed grade 0, bilaterally. Pain and touch sensation was absent below T1, including perineal sensation. After intensive rehabilitation in January 2017 for 1 month, overall functions were slightly improved, but still unable to sit without hands support. Cystometry on March 24th, 2017 showed bladder capacity of 220 mL and the intravesical pressure of 74 mm H_2O when clinical of autonomic dysreflexia (AD) was presented.

After 10 sessions (one time per week) of combined high-frequency (10–20 Hz) transcranial, trans-spinal and peripheral magnetic stimulation, bladder diary showed 500 mL. Capacity before AD was developed, without any sign of urinary tract infection. Furthermore, sitting balance was significantly improved, without hands support for at least 10 s. The pinprick sensation test was improved next two dermatomes. The electrical feeling was reported in his left thigh during leg-motor cortex (Cz) transcranial magnetic stimulation. Breathing was subjectively 50% improvement.

26.6 Summary

Magnetic stimulation has been shown to be a safe and well-tolerated procedure in many conditions including neurogenic bladder. A combination of standard rehabilitation and magnetic stimulation is the novel strategy to maximize neurogenic bladder outcomes and promising research is under way that could lead to conquering of the disability.

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Drug Treatment

27

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27.1 Overview

Karl-Erik Andersson

27.1.1 Classification of Drugs for NLUTD Treatment and Principles of Medical Therapy

Neurogenic lower urinary tract dysfunction (NLUTD) is a heterogeneous combination of symptoms and urodynamic findings that are the result of neurological injury to the bladder (Fig. 27.1) [1–4]. The patterns of bladder storage and voiding disturbances depend on the lesion of neurologic lesion (Fig. 27.2). Patients often have incontinence, urgency, frequency and/or impaired bladder emptying. Urodynamically, there is often poor bladder wall compliance, neurogenic detrusor overactivity (NDO) and/or detrusor sphincter dyssynergia (DSD) which may result in morphological changes in the bladder wall, such as trabeculations and diverticulae. NLUTD can be found in 85–90% of patients with spinal cord injury (SCI), with urinary incontinence occurring in more than 50% NLUTD also occurs in 50–80% of patients with multiple sclerosis (MS), in 27–64% of patients with Parkinson's disease, and in over 95% of patients with spina bifida [3]. It also occurs frequently with many other neurological conditions such as after stroke, transverse myelitis, and autonomic disorders [1–4].

NLUTD has many clinical presentations with the most severely affected patients having urinary retention requiring catheterization for bladder emptying. Neurogenic detrusor overactivity, NDO (NDO has replaced the previous term detrusor hyperreflexia) is defined by the international Continence Society (ICS) as "a urodynamic observation of involuntary detrusor contraction(s) during the bladder-filling phase, which may be spontaneous or provoked, due to an underlying relevant neurologic condition" [5]. Incontinence is often the most bothersome problem in NLUTD patients and can lead to poor hygiene, skin breakdown, and social isolation. NDO may include urinary incontinence episodes that are not associated with urgency or any other sensation related to bladder filling. Patients can have sustained high bladder pressures from DO or low bladder compliance, which especially when combined with detrusor sphincter dyssynergia (DSD) can lead to upper tract deterioration, such as vesico-ureteric reflux, hydronephrosis, renal impairment and eventually end-stage renal disease [1–4].

The main objectives for current strategies in the treatment of NDO are (1) protection of the upper urinary tract, (2) improvement of urinary continence, (3) restoration of the lower urinary tract function (or parts of it), and (4) improvement in the patient's quality of life (QoL) [6].

There are several oral and intravesical pharmacotherapeutic agents that have been evaluated to treat DO and diminished bladder compliance in the NLUTD [7, 8]. The less severe forms of NLUTD are more commonly seen in patients with Parkinson's disease, stroke, and MS. These patients maintain neurological connectivity between the bladder and pontine micturition centre and can void volitionally, but may still have urgency, frequency, urgency incontinence, and

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_27

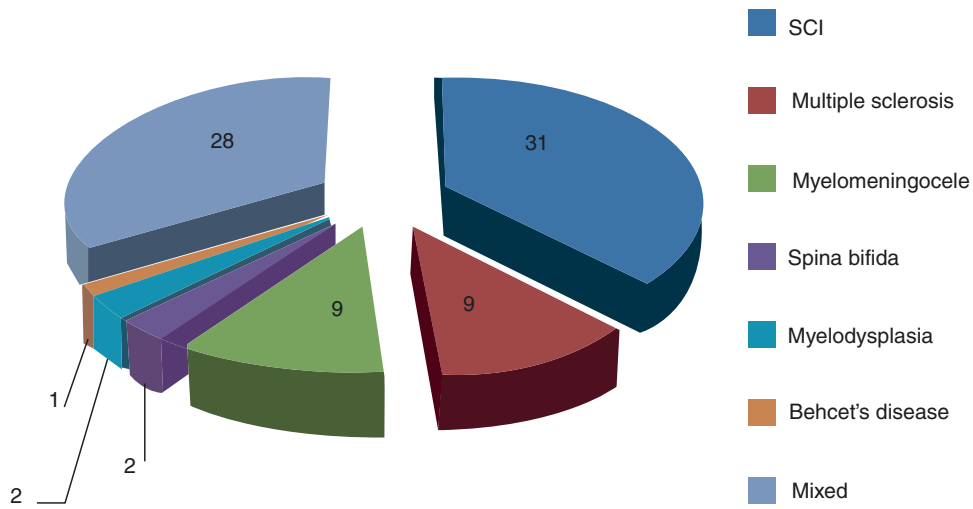

Fig. 27.1 Neurogenic lower urinary tract dysfunction: a heterogeneous combination of symptoms and urodynamic findings that are the result of neurological injury to the bladder

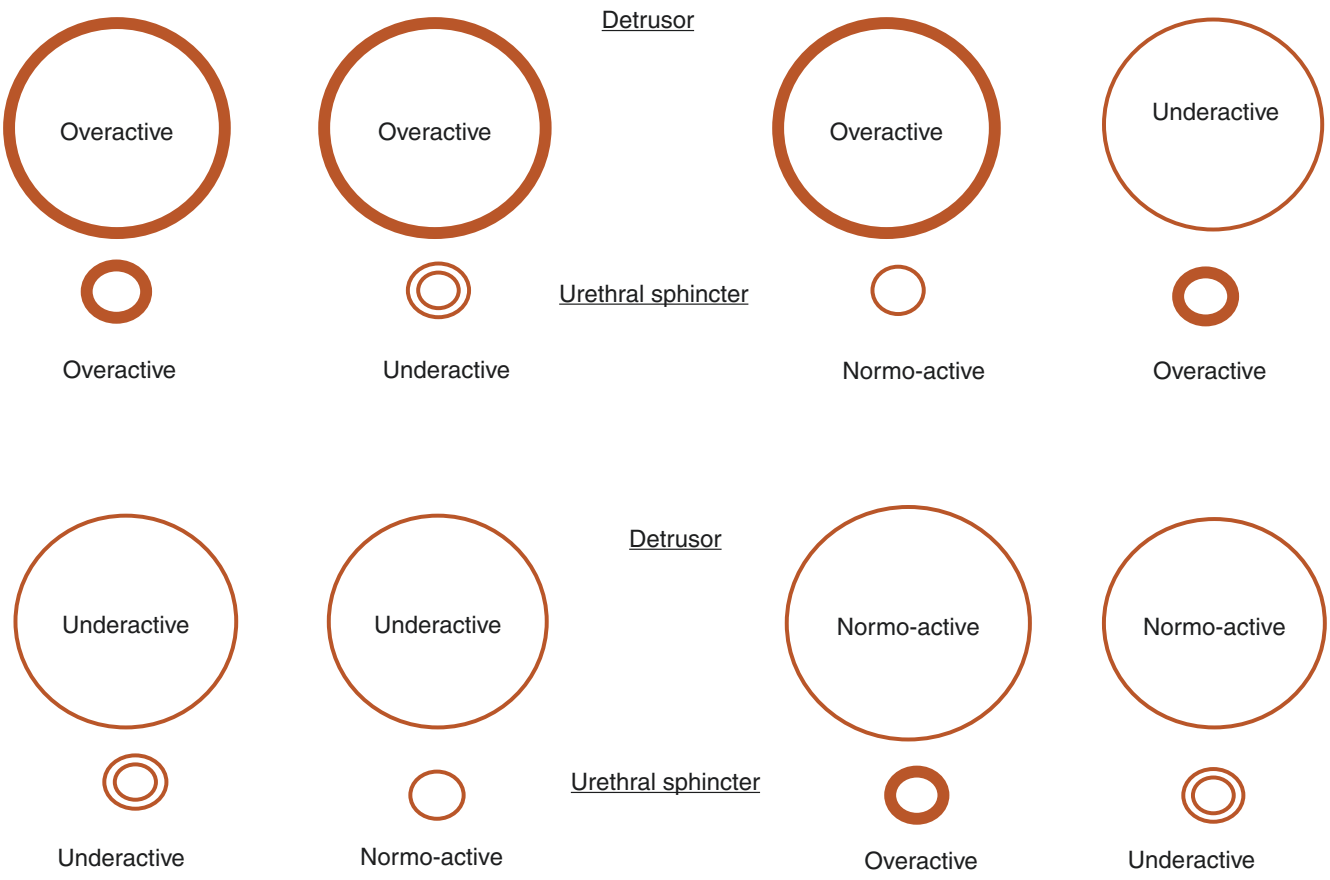

Fig. 27.2 The patterns of bladder storage and voiding disturbances in patients with NLUTD

DO. These patients are often at particularly high risk of urinary retention since they may at baseline have elevated PVR due to poor bladder contractility, functional outlet obstruction or benign prostatic hyperplasia. This is a particularly important consideration with any treatment of their DO. These treatments may exacerbate poor emptying and in these patients, preservation of the ability to void is desirable.

27.2 Detrusor Relaxing Agents

Karl-Erik Andersson

The main reasons for intervention with drug therapy are high storage pressures and DO, or a need for treating or preventing urinary tract infections (UTI). Early management is focused on optimization of bladder storage function to pre-

vent irreversible injury to either the upper or lower urinary tracts. Drugs are also used for improving urinary flow, lowering the post void residual volume (PVR), to fight vesicoureteric reflux (VUR), or for reducing spasticity. Other possible indications for drug therapy are urinary incontinence, and the management of stone disease.

27.2.1 Antimuscarinic Drugs

Antimuscarinic drugs competitively antagonise muscarinic acetylcholine receptors, resulting in detrusor relaxation, lower intravesical pressures, and reduced storage symptoms. The M_2 muscarinic receptor is widely distributed throughout the detrusor, urothelium, and suburothelium, whereas the M_3 receptor is functionally the most relevant subtype in the bladder [9, 10]. It has been proposed that stimulation of M_2 receptors can also directly elicit bladder contraction under pathological conditions [11, 12], but such observations have not been confirmed by other investigators using distinct methodological approaches [13, 14]. It appears that the contribution of muscarinic mechanisms to the overall regulation of bladder contractility decreases in favour of non-cholinergic mechanisms under pathological conditions [15–17]. These observations may help to explain the moderate efficacy of muscarinic receptor antagonists relative to placebo in controlled clinical studies [10].

Datta et al. [18] found decreased suburothelial muscarinic receptor immunoreactivity (significant for muscarinic receptors 1 and 3) in biopsies from patients with neurogenic DO vs controls. This was normalized after onabotulinumtoxin A treatment. If there are changes in the number or sensitivity of muscarinic receptors in the bladder is unclear, and if there are, the clinical relevance is uncertain. Some studies have reported that in NLUTD patients, the dosages of antimuscarinics can be doubled without any increase in adverse effects (see below). In normal individuals, a doubling of dosage also doubles the number of systemic adverse effects. If there are any changes in the muscarinic receptor system in NLUTD patients resulting in an increased tolerability to antimuscarinic agents has not been established.

Since the introduction of oxybutynin, several newer antimuscarinic agents have appeared on the market [19]. Systematic reviews have not concluded superiority of one agent over others and suggest that the only difference between drugs is their side-effect profiles [20], and prescribing patterns are often determined by local guidelines. Especially in older people the patient should be reviewed before prescribing an antimuscarinic agent, because there is evidence to suggest that cumulative use of agents with antimuscarinic properties is associated with increased risk of cognitive impairment and possible development of dementia [21–23]. Some studies have not been able to confirm such effects [24, 25]. Agents that do not readily cross the blood–brain barrier or have relatively high affinity for the muscarinic receptors of the bladder would theoretically have less effect on cognition. However, evidence supporting these considerations in clinical practice is limited, and caution is advised when using an antimuscarinic agent in the susceptible neurological patient. Measurement of the PVR volume should be done preferably before antimuscarinic treatment is started. Furthermore, if there is reason to suspect that a patient already established on treatment has developed incomplete bladder emptying (e.g., poor response to antimuscarinic drugs), or is reporting recurrent UTIs, the PVR volume should be measured again. In many patients, the judicious combination of antimuscarinic treatment plus intermittent self-catheterisation provides the most effective management for neurogenic LUT dysfunction. Madhuvrata et al. [20] performed a meta-analysis of randomised controlled trials (RCTs) to assess the efficacy, safety, and tolerability of (1) anticholinergic drugs compared with placebo, (2) one type of anticholinergic drug compared with another type of anticholinergic drug, (3) different doses and preparation of the same anticholinergic drug, and (4) different routes of administration of anticholinergic drugs in patients with NDO. They found that compared with placebo, anticholinergic treatment in patients with NDO is associated with better patient-reported cure/improvement and significant reduction of maximum detrusor pressure; however, there is a higher incidence of adverse events. None of the anticholinergic drugs or different dosages assessed in this review was superior to another.

Madersbacher [26] found that the most frequently reported adverse effect (AE) was dry mouth, higher incidence rates are reported for oxybutynin IR compared with trospium chloride IR [19], tolterodine [16] and propiverine [20]. Higher doses of AM were not necessarily associated with higher rates of AE [22, 24, 27]. In 21 patients with NDO, Horstmann et al. [27] doubled the recommended dosage of tolterodine and trospium to either 8 mg of tolterodine ER [2 × 4 mg (n = 11)] or 90 mg of trospium [3 × 30 mg (n = 10)]. The follow-up was monitored by a bladder diary and urodynamic evaluation. Sixteen patients significantly decreased their incontinence episodes from 8–12 episodes before to 0–2 episodes during the doubled treatment. The reflex volume increased from 202 ± 68 to 332 ± 50 ml. Cystometric capacity enlarged from 290 ± 56 to 453 ± 63 ml ($P < 0.001$). One patient had to stop the medication because of intolerable side effects and five patients did not experience satisfactory benefit. Amend et al. [28] reported that with combined high-dosage antimuscarinic medications, 85% of the patients who previously demonstrated unsatisfactory outcome with dosage-escalated monotherapy were treated successfully. The appearance of side-effects was comparable to that of normal-dosed antimuscarinics. Three long-term stud-

ies [35–37] reported AE rates of up to 13% [35], and drop-out rates of 27%, due to side effects or unsatisfactory outcomes [36].

27.2.1.1 Oxybutynin: Overview, Effects and Side Effects

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Pharmacology

Oxybutynin is a tertiary amine that is well absorbed, and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The plasma half-life of the oxybutynin is approximately 2 h, but with wide interindividual variation. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [29], and occurs in high concentrations after oral administration. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [30]. Oxybutynin has several pharmacological effects *in vitro*, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. The drug was shown to have slightly higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors, but the clinical significance of this is unclear.

Efficacy and Side Effects

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer antimuscarinic agents have been compared to it once efficacy over placebo has been determined. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available [31, 32].

Immediate-Release Oxybutynin (OXY-IR).

Several controlled studies have shown that OXY-IR is effective in controlling DO, including neurogenic DO [19, 33]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [34] summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24 h was 33% (data on placebo not presented). The overall subjective improvement rate was reported as 74% (range 61–100%). The mean percent of patients reporting an adverse effect was 70 (range 17–93%).

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [35]; no changes were found.

Extended Release Oxybutynin (OXY-ER)

This formulation was developed to decrease liver metabolite formation of DEO with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy [36]. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 h distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [37].

The effects of OXY-ER have been well documented both in patients with OAB and NDO [19, 38], but is not without side effects. Several studies have documented the possibility that oxybutynin may have negative effects on *cognitive functions*, particularly in the elderly population, but also in adults and in children [39, 40]. This factor should be taken into consideration when prescribing the drug.

27.2.1.2 Tolterodine: Overview, Effects and Side Effects

Karl-Erik Andersson

Pharmacology

Tolterodine is a tertiary amine, rapidly absorbed and extensive metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound, and significantly contributes to the therapeutic effect of tolterodine. Both tolterodine and 5-HMT have plasma half-lifes of 2–3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1–2.4% of the dose; 5–14% of 5-HMT is eliminated in the urine. The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT, implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [19, 41–43].

Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [44].

Efficacy and Side Effects

Several randomised, double blind, placebo-controlled studies on patients with OAB/DO (both idiopathic and neurogenic DO), have documented a significant reduction in micturition frequency and number of incontinence episodes [41–43]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness [19].

Watanabe et al. [45] evaluated the efficacy of TOLT-ER 4 mg/day for the treatment of NDO and/or low-compliance bladder by assessing urodynamic parameters in 46 patients (25 male, 21 female; mean age 57.6 ± 20.7 years) with NDO (n = 39) and/or low-compliance bladder (n = 7) in a 12-week single-arm study. They found that bladder capacity at first sensation and maximum cystometric capacity increased significantly, by an average of 36.8 mL and 82 mL, respectively. In patients with low-compliance bladder, bladder compliance increased significantly. Overactive bladder symptom score, International Consultation on Incontinence Questionnaire-Short Form score, number of voids (per 24 h and night-time), number of urgency episodes in 24 h, number and amount of leaks in 24 h, and amount of mean and maximum voided volumes all decreased significantly after treatment.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs [19, 41–43]. Dry mouth and constipation are the most frequently reported adverse events. The incidence of adverse CNS events with tolterodine was low and similar to that of placebo. Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo was performed. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 ms absolute QTc or 60 ms change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval [46].

27.2.1.3 Trospium: Overview, Effects and Side Effects

Karl-Erik Andersson

Pharmacology

Trospium is a quaternary ammonium compound with a biological availability less than 10% [47, 48]. The drug has a plasma half-life of approximately 20 h, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [49]. Whether or not it contributes to the clinical efficacy of the drug remains to be established. Trospium has no selectivity for muscarinic receptor subtypes.

Trospium is not metabolized by the cytochrome P450 enzyme system. It is expected to cross the blood-brain to a limited extent since it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain. This was demonstrated by Staskin et al. [50], showing that trospium chloride levels in CSF samples were undetectable on Day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values. Clinically, trospium seems to have no negative cognitive effects [50, 51].

Efficacy and Side Effects

Several RCTs have documented positive effects of trospium both in NDO and OAB [19] In a placebo-controlled, double blind study on patients with neurogenic DO [52], the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [53].

The effect of trospium in urgency incontinence has been documented in several RCTs [54–56]. Zinner et al. [56] treated 523 patients with symptoms associated with OAB and urgency incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo controlled trial. Dual primary end points were change in average number of toilet voids and change in urgency incontinent episodes per 24 h. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 h (−2.37) and urgency incontinent episodes 59% compared to placebo (−1.29; 44%). It significantly increased average volume per void (32 ml; placebo: 7.7) ml, and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (−0.43; placebo: 0.17)—and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%).

Dose escalation seems to improve therapeutic efficacy. In a 12-week, randomised, double-blind, phase IIIb study including 1658 patients with urinary frequency plus urgency incontinence received trospium chloride 15 mg TID (n = 828) or 2.5 mg oxybutynin hydrochloride TID (n = 830). After 4 weeks, daily doses were doubled and not readjusted in 29.2% (242/828) of patients in the trospium group, and in 23.3% (193/830) in the oxybuytynin group, until the end of treatment. At study end, there were no relevant differences between the "dose adjustment" subgroups and the respective "no dose adjustment" subgroups (trospium: P = 0.249; oxybutynin: P = 0.349). After dose escalation, worsening of dry mouth was higher in both dose adjusted subgroups compared to the respective "no dose adjustment" subgroups (P < 0.001). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups [57].

An extended release formulation of trospium allowing once daily dosing, has been introduced [58], and its effects tested in controlled trials [19]. These studies demonstrated similar efficacy as found with previous formulations, but include experiences in e.g., elderly patients (>75 years), obese patients, and in patients who use multiple concomitant medications. In the pooled analysis of 2 large phase III trials (n = 1027), trospium chloride extended release 60 mg once daily significantly improved micturition and UUI episodes per 24 h compared to placebo [59]. Furthermore, trospium was superior to placebo in OAB symptom composite score, urgency episodes and mean voided volume. Dry mouth and constipation were the two commonest adverse events being 10.7% and 8.5% with trospium compared to 3.7% and 1.5% with placebo.

27.2.1.4 Propiverine: Overview, Effects and Side Effects

Helmut Madersbacher

Pharmacology

Propiverine, a tertiary amine, has combined antimuscarinic and calcium antagonistic actions [60]. The importance of the calcium antagonistic component for the drug's clinical effects has not been established yet. Propiverine has no selectivity for muscarinic receptor subtypes [19]. The drug is rapidly absorbed (max. 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Several active metabolites are formed, which quantitatively and qualitatively differ from the mother compound [61].

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Mürtz [62].

Efficacy and Side Effects

The efficacy of propiverine in neurogenic detrusor overactivity has been evaluated in several studies. In a randomized, double-blind, prospective multicentre clinical study Stöhrer et al. [26] compared the efficacy and tolerability of propiverine and oxybutynin in patients with neurogenic detrusor overactivity. Propiverine and oxybutynin were equally effective in increasing bladder capacity and lowering bladder pressure. The trend for better tolerability of propiverine compared to oxybutynin achieved significance for dryness of the mouth (LOE1). Propiverine hydrochloride has also been shown to be effective even in some cases unresponsive to other antimuscarinics. The low incidence rate of adverse events evidenced a favourable risk-benefit profile of propiverine hydrochloride (LOE3).

In 2013 McKeage [63] published a review on Propiverine, of its use in the treatment of adults and children with overactive bladder associated with idiopathic or neurogenic detrusor overactivity, as well as in men with lower urinary tract symptoms.

Propiverin is nowadays also available in an extended release (ER) formulation. Comparing patients with neurogenic detrusor overactivity in a double-blind randomized multi-centre study, comprising 66 patients with proven NDO, Stöhrer et al. [64] demonstrated, that both galenic formulations are equi-effective, however following propiverine ER 45 mg once daily higher continence rates compared with propiverine ER 15 mg t.i.d were achieved, indicating most probably more balanced plasma-levels with the ER formulation. A slight tendency for superior tolerability outcome with ER compared with IR was demonstrated, however, it did not reach statistical significance.

According to data on file (Apogepha Company, Dresden) the metabolites of propiverine are more hydrophilic and pass therefore the blood-brain-barrier only to a limited extent. This finding goes along with some clinical data: Sakakibara et al. [65] demonstrated in a case series comprising 26 cognitively impaired elder persons (mean age 70.8 years) already on 5 mg donepezil for memory problems that additional intake of 20 mg propiverine per day did not cause any changes in cognition measured by MMSE (mini-mental state examination, 0–30 scale) and ADAS-cog (Alzheimer's disease assessment state cognitate subscale, 0–70).

In another non-interventional study, comprising 201 OAB patients, age > 70 years, Oelke et al. [66] could show that propiverine 30 mg ER did not cause any signs of cognitive alteration measured with the help of MMSE and PPBC (patient perception of bladder condition) during a 12 weeks period. Therefore, propiverine is effective (comparable with oxybutynin), but with fewer side-effects (dry mouth rate), moreover, no CNS side-effects are reported so far, measured by MMSE, ADAS-cog and PPBC, also in patients being already on cholinesterase inhibitors for memory problems.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [67, 68], with a low incidence rate of adverse events (<1.5%).

Propiverine has a documented beneficial effect in the treatment of neurogenic OAB/DO, and has an acceptable side effect profile [19].

27.2.1.5 Solifenacin Succinate: Overview, Effects and Side Effects

Waleed Altaweel

Overactive bladder syndrome (OAB) is defined by International Continence Society as symptoms of urgency with or without urge incontinence and is usually associated with frequency and nocturia [68]. It affects millions of people worldwide, with an increasing prevalence in the elderly [69]. Despite this, large numbers of patients remain untreated either due to reluctance to report problems to their physician or because of myth in societies that it is part of normal ageing phenomenon and there is no treatment for these symptoms [70]. The treatment options for OAB include behavioral, pharmacological and surgical therapy. Antimuscrinic drugs are the mainstay of pharmacological therapy for OAB. Newer antimuscrinic agents are long acting and have better side effect profile as compare with short acting antimuscrinic drugs. Solifenacin succinate is a once daily dozing, long acting antimuscrinic drug that is discussed in this chapter.

Chemical Structure

Solifenacin is the succinic acid salt of azabicyclo-phenyl-isoquinolinecarboxylate and has molecular weight of 480.55 g/mol and molecular formula of $C_{27}H_{32}N_2O_6$. It is a tertiary amine with antimuscrinic properties. Chemical structure of solifenacin [71] is shown in Fig. 27.3.

Pharmacokinetics

Solifenacin is highly protein bound (98%) and is extensively metabolized through hepatic metabolism via cytochrome P450 (CYP) 3A4 with only little amount (7%) being excreted unchanged in urine. Its peak plasma concentration of 24.0 and 40.6 ng/ml are reached 3–8 h after long term oral administration of a 5 or 10 mg solifenacin dose, respectively [72]. A study conducted in young healthy individual, time to maximum plasma concentration (T_{max}) ranged from 3.3 h (20 mg dose) to 4.8 h (5 mg dose), and mean $t_{1/2}$ ranged from 40.2 to 102.6 h for solifenacin in single dose study while mean T_{max} ranged from 2.9 h (20 mg dose to 5.8 h (5 mg dose) and mean $T_{½}$ ranging from 45.0 to 64.8 h observed in multidosing study (5, 10, 20 and 30 mg) [73].

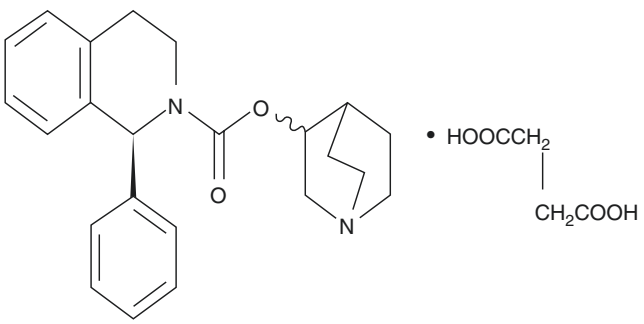

Fig. 27.3 Chemical structure of solifenacin

Solifenacin displays a higher exposure and a prolonged half-life in patients with renal impairment, especially severe. Therefore, while no special cautions are necessary for patients with mild/moderate renal impairment, patients with severe renal impairment should receive no more than 5 mg solifenacin once daily [74]. Similarly moderate hepatic impairment [defined as a Child-Pugh score of 7–9] influenced solifenacin pharmacokinetics and dosage more than 5 mg is not recommended in these patients [75].

Mechanism of Action

Solifenacin is a competitive cholinergic receptor antagonist, selective for the M3 receptor subtype. The binding of acetylcholine to these receptors, particularly M3, plays a critical role in the contraction of smooth muscle. Human body has five subtypes of muscarinic receptors (M1–M5) [76]. The M2 and M3 receptors subtypes exert an important role in bladder contraction [76, 77]. In almost all of studies on human bladder or other species, independent of the technique used whether radioligand binding or immunoprecipitation, M2 receptors appears to be outnumbered M3 by about 3:1 and in some species especially in rat, the ratio is even greater at 9:1 [78]. Although M2 receptors are more concentrated than M3 receptors in human bladder, bladder contraction is primarily because of M3 receptors [79]. The M3 receptor subtypes couple to $G_{q/11}$ and activate phospholipase C to induce inositol phosphate turnover, while the M2 receptor subtypes inhibit adenylate cyclase via Gi proteins [80, 81]. This is the signaling mechanism responsible for the direct contractile responses to muscarinic agonists in this detrusor muscle as shown in figure (Fig. 27.4).

Although role of M2 receptor in detrusor contraction is not clearly known, it is thought that stimulation of M2 receptors may oppose the sympathetic relaxation thereby causing detrusor contraction [82]. In a normal bladder, detrusor contraction is mainly mediated by M3 receptors but in disease state like neurogenic bladder or certain organ transplant donor, bladder contraction is mediated by M2 receptors [83].

Drug Interactions

Solifenacin is metablized in the liver through CYP3A4 pathway. Pharmacokinetics of solifenacin may alter by inducers or inhibitor of this isoenzyme. Therefore it is recommended that dose should not be exceeded more than 5 mg/day when therapeutic doses of potent CYP3A4 inhibitors are co-administered [71].

Swart PJ et al. [84] found that plasma concentrations of solifenacin were higher when it was co-administered with

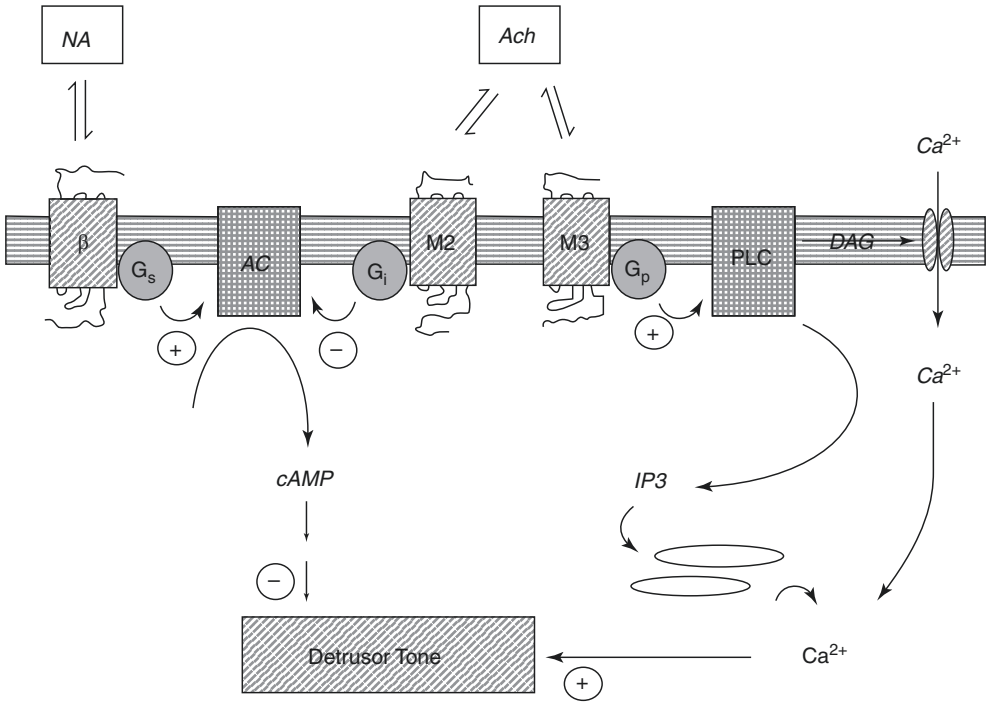

Fig. 27.4 Second messenger systems for M2- and M3-muscarinic receptors. Acetylcholine (Ach) stimulates M3-receptors to cause direct detrusor contradiction via the second messengers inositol triphosphate (IP3) and diacylglycerol (DAG). Acetylcholine also induces a contraction indirectly by inhibiting the production of cyclic AMP and reversing the relaxation induced by β-adrenoceptors following stimulation by noradrenaline (NA). All three receptors are coupled to their respective second messenger systems via G-proteins (Gs Grmi Gq/11)

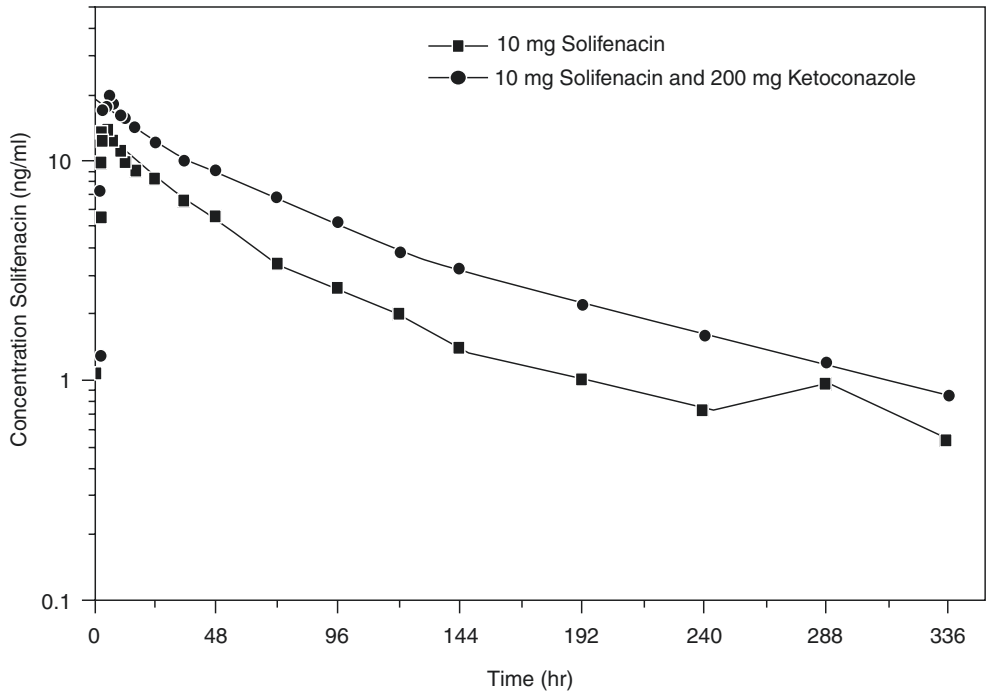

Fig. 27.5 Mean plasma concentration-versus-time profiles for oral solifenacin alone and solifenacin plus ketoconazole

ketoconazole 200 mg/day as compared to when it was used alone (Fig. 27.5). Pharmacokinetics was assessed by measurements of maximum plasma concentration (Cmax), time to Cmax, area under the curve (AUC), and elimination half-life ($t_{1/2}$). Co-administration resulted in 1.43 times increase in Cmax and almost 2 times increase in AUC. The mean $t_{1/2}$ of solifenacin was increased from 49.3 to 77.5 h. The median T_{max} of solifenacin remained unchanged at around 6 h regardless of the co-administration of ketoconazole.

Taekema-Roelvink and colleagues [85] studied the effect of SOL on the pharmacokinetics of an oral contraceptive (OC) containing ethinyl estradiol (EE) 30 μg and levonorgestrel (LNG) 150 μg in a double blind placebo-controlled,

2-period cross-over study. Twenty-four healthy women (mean age 26.3 years; mean weight 64.0 kg) who received combined OC for two 21-days cycle, then separated by 7 days washout. On day 12 of each cycle subjects were started a with solifenacin 10 mg once a day for 10 days, which is two times the suggested starting dose or placebo. Subjects were crossed over to other treatment arm for the second cycle. Pharmacokinetic interaction between SOL and OC containing EE and LNG were not found significant. Suppression of LH or FSH was not altered by SOL in this study.

Michel and colleagues [86] evaluated interaction of SOL with warfarin; digoxin and salicylates in healthy subjects. They concluded that administration of 10 mg of solifenacin once daily was not interacted with single 25 mg dose of warfarin or a 0.25 mg of loading dose of digoxin or followed by 1.25 mg of dose.

Clinical Trials

Govier and colleagues [87] investigated the efficacy and safety of solifenacin 10 mg once daily dosing in his multicenter double blind placebo controlled, phase III pivotal trial. It involved 634 adult patients with OAB symptoms were randomized to either solifenacin 10 mg (n = 318) once daily or placebo (n = 316) over a 12 weeks. Patients were advised to fill micturition diary for the 3 days preceding each follow up clinic visit (week 4, 8 and 12). The study investigated the changes from baseline in frequency of micturition, urgency, incontinence and nocturia episode/24 h in 3 day diary. SOL significantly reduced mean number of frequency of micturition, urgency and incontinence episode/24 h ($p < 0.001$ for all variable versus placebo). This improvement were observed at 4 weeks and continued at the end of 12 weeks. Side effects were typically anticholinergic in nature and were mild or moderate in severity. So it was concluded in trial that solifenacin 10 mg once daily was effective in treating major OAB symptoms and well tolerated.

Another similar randomized, double blind, placebo and propiverine controlled trial of the once daily SOL 5 or 10 mg conducted by Yamaguchi et al. [88] in Japanese adult patients with overactive bladder. A total of 2049 patients were enrolled from 155 centers in Japan. After 2 weeks of placebo run in period and non-compliance after randomization, total of 1584 patients were treated. Primary objective of study was to determine superiority of SOL to placebo and non-inferiority to propiverine 20 mg in effect on reducing OAB symptoms. Quality of life was assessed by using king' health questionnaire consisting of 21 questions in 9 domains. Significant reduction in mean number of void/24 h were noted with SOL 5 mg at −1.93 (1.97), and 10 mg at −2.19 (2.09), and propiverine 20 mg, at −1.87 (2.70), than with placebo at −.94 (2.29) [$p < 0.001$ for all]. All other variables like urgency, nocturia, urgency incontinence were significantly improved with SOL and propiverine than placebo. The study design, mean change from baseline is shown in Figs. 27.6 and 27.7.

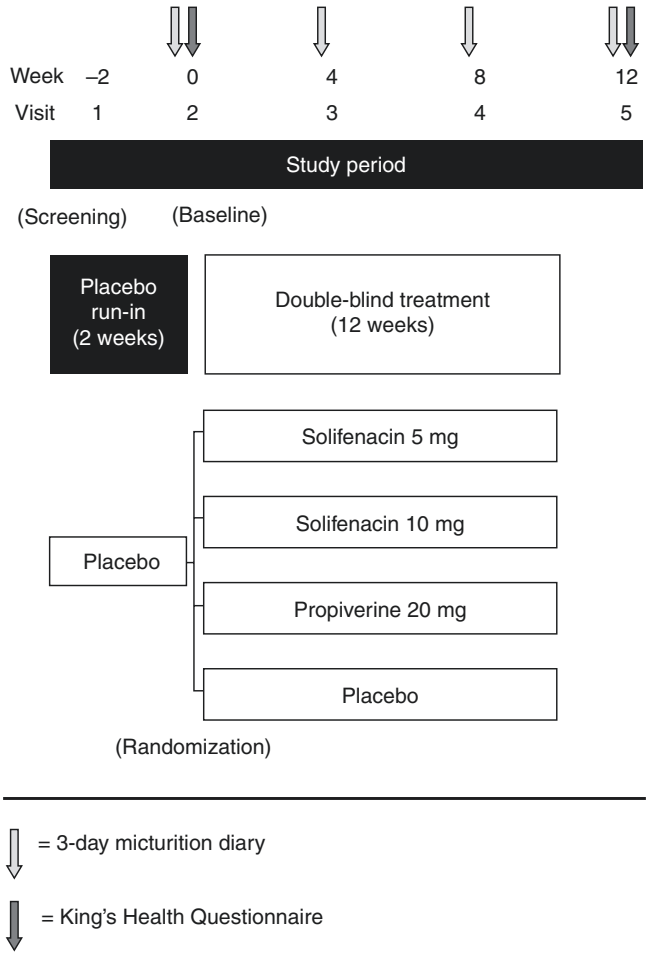

Fig. 27.6 The study design

Chapple and colleagues [89] reported on an international, multicenter, double blind randomized trial that involved 1281 patients who had overactive bladder symptoms (OAB) for >3 months were included in study. 1077 patients were treated and 1033 patients were evaluated for efficacy. After a placebo run in for 2 weeks, equal number of patients were randomized to 12 weeks of double blind treatment with tolterodine (2 mg twice daily), to placebo, or to solifenacin (5 or 10 mg once daily). Patients were examined at baseline, 4 weeks, and 12 weeks with voiding diaries. The Efficacy variables included change from baseline in the mean number of episodes of urgency, incontinence and urge incontinence. The voiding diaries were completed for 3 days before each follow-up visit. Adverse events were recorded and classified according to severity and relationship with study medications.

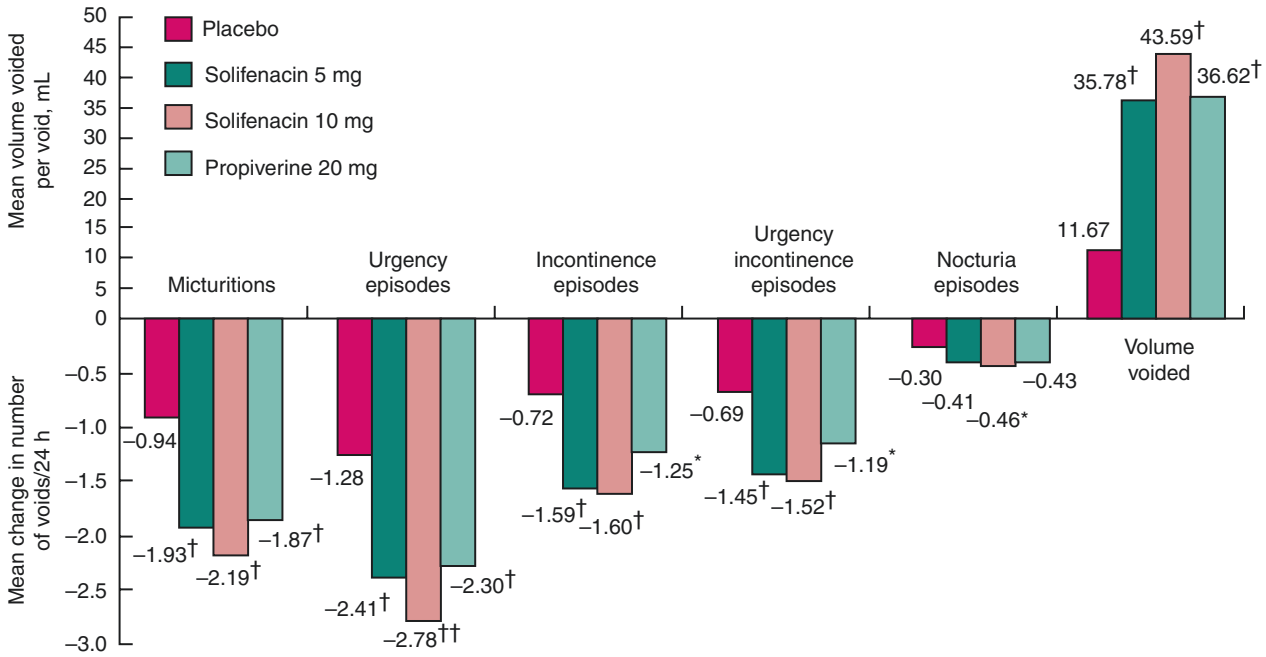

Fig. 27.7 The mean change in the number of voids/24 h, other urinary episodes and volume voided/void from baseline to endpoint (for patients with a full analysis). P < 0.025 and †P < 0.001 vs placebo; P < 0.025 vs propiverine 20 mg

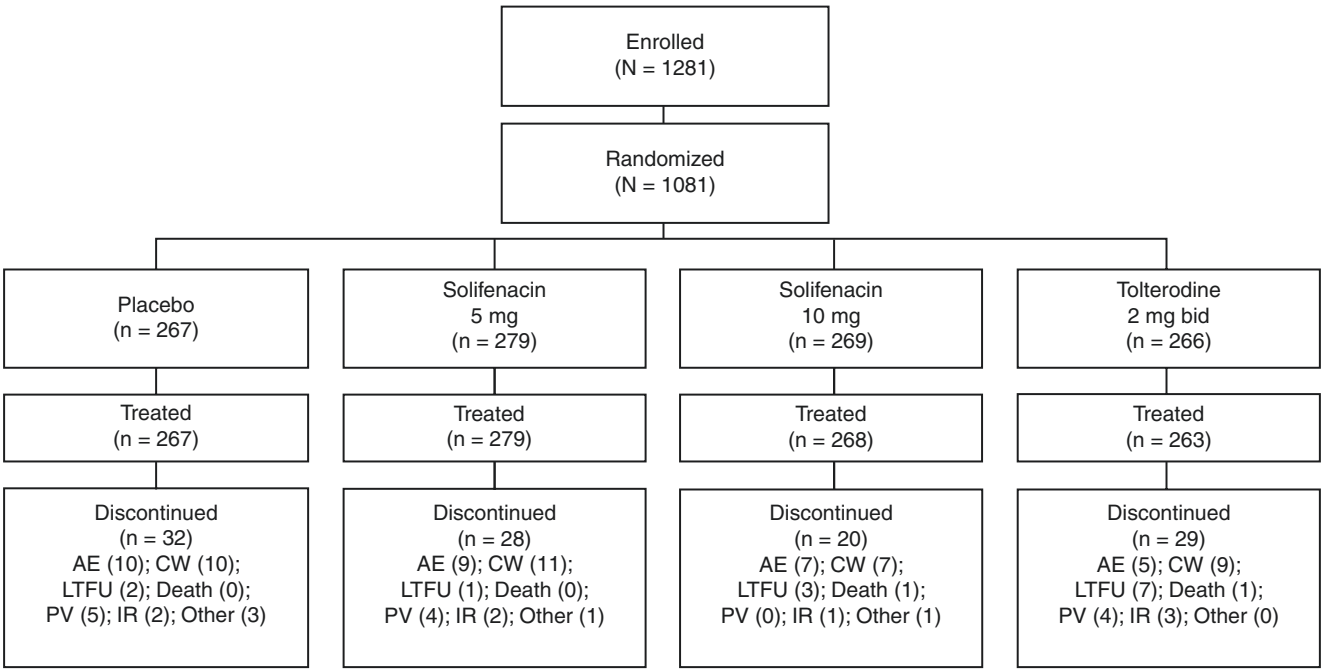

Fig. 27.8 Disposition of study patients

Patients treated with solifenacin reported a significant decrease from baseline and number of urgency episodes per 24 h compared with placebo group (placebo, 33%; 5-mg solifenacin, 52%; 10-mg solifenacin, 55%; p < 0.001). Solifenacin group demonstrated a statistically significant reduction in all incontinent episodes compared to placebo: 5-mg solifenacin, −1.42 episodes per day, p = 0.008; 10-mg solifenacin, −1.45 episodes per day, p = 0.0038). Patient disposition, mean change in urgency, urgency incontinence and adverse events are shown in Figs. 27.8, 27.9 and 27.10, and Table 27.1 respectively.

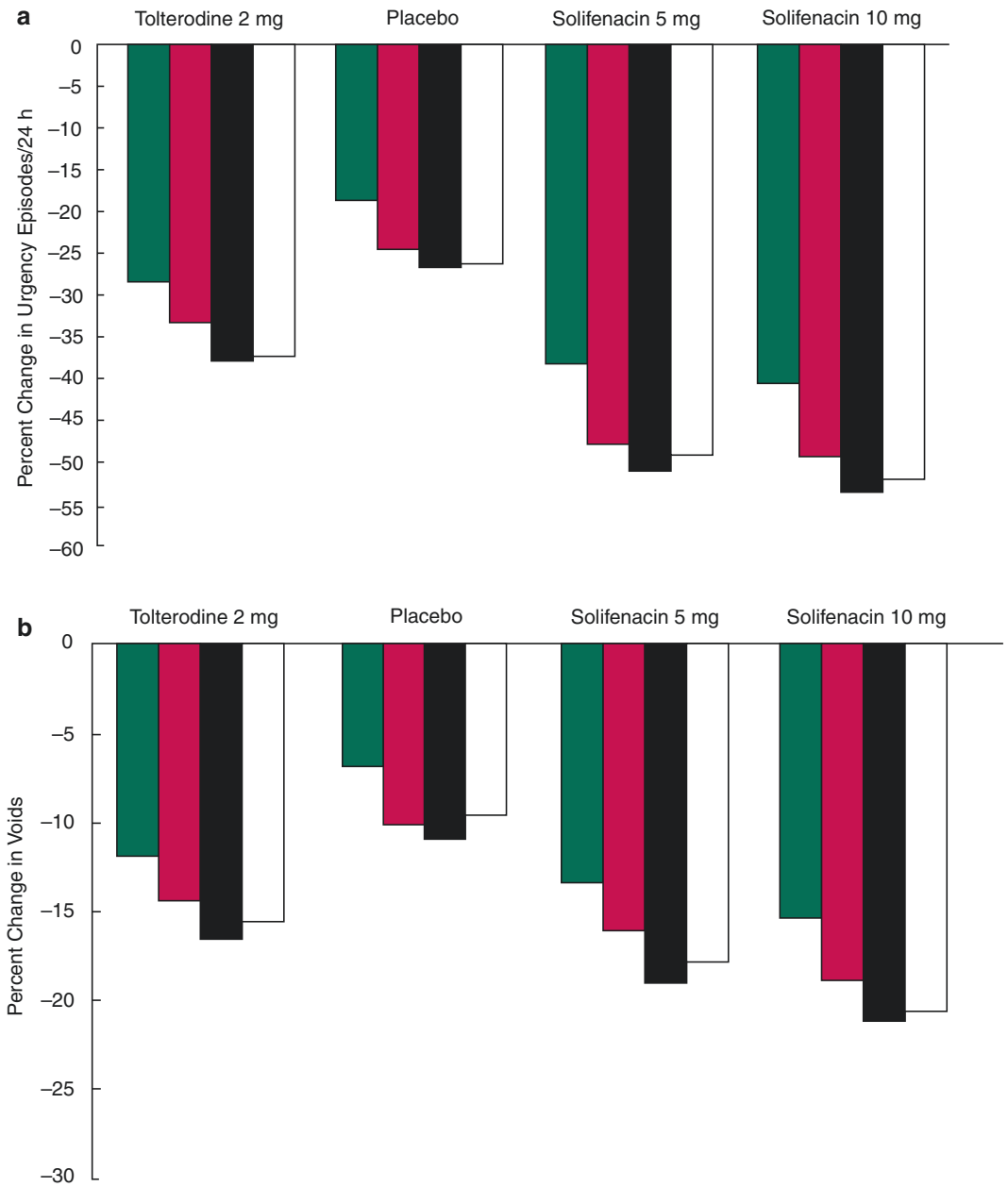

Fig. 27.9 Percentage change from baseline to endpoint in **a**, the mean number of urgency episodes per 24 h, and **b**, the mean number of voids/24 h. In each the green bar is week 4, the red bar week 8, the black bar week 12 and the open bar the endpoint

These preliminary studies lead to flexible dosing trial of solifenacin (Solifenacin and Tolterodine as an active comparator in a Randomized (STAR) trial) reported by Chapple and colleagues [90]. In this head to head clinical trial, extended release tolterodine was compared with dose flexible solifenacin. Patients could escalate their dose of solifenacin from 5 to 10 mg after consultation with physician. Patients in tolterodine group were escalated from 4 mg daily to 4 mg tolterodine plus 4 mg placebo. Study design of this trial is shown in Fig. 27.10.

Regarding primary end point of decrease in micturition frequency, solifenacin was found to be as effective as tolterodine ($p = 0.004$, noninferiority). Solifenacin was more effective in terms of improvement in secondary outcome measures like urge incontinence ($p = 0.001$), overall incontinence ($p = 0.006$), and urgency ($p = 0.035$) than patients who were

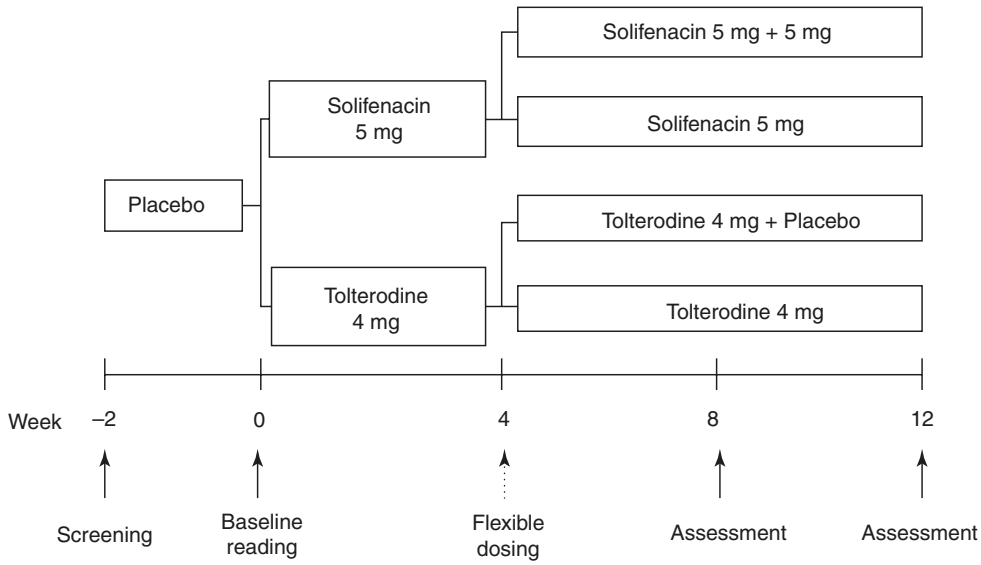

Fig. 27.10 Study design of STAR Trial

Table 27.1 The number of patients discontinuing treatment before study completion and the treatment related major anticholinergic side-effects (1077 patients)

Characteristics	Placebo (n = 267)	Solifenacin 5 mg (n = 279)	Solifenacin 10 mg (n = 268	Tolterodine 2 mg twice daily (n = 263)	Total (n = 1077)
Discontinuing					
Adverse events	10	09	07	05	31
Consent withdrawal	10	11	07	08	36
Lost to follow-up	02	01	02	06	11
Protocol violation	05	04	0	03	12
Insufficient response	02	02	01	03	08
Patients died	0	0	01	01	02
Other	03	02	01	0	05
Total	32	28	19	26	105
Major side effects:					
Dry mouth	13	39 57		49	
Constipation	5	20 21		07	
Blurred vision	7	10 15		04	

treated with 4 mg of extended release toterodine as shown in Figs. 27.11 and 27.12.

Furthermore, 59% of patients treated with solifenacin who were incontinent at baseline became continent by endpoint of study, compared with 49% of patients treated with tolterodine ER who were incontinent at baseline (p = 0.006). Overall, 34 (5.9%) and 44 (7.3%) patients discontinued study medication for any reason on solifenacin and tolterodine ER, respectively.

Cardozo and colleagues [91] presented a multicenter, multinational, randomized, double-blind, placebo controlled trial on 1091 enrolled patients in which 907 patients were treated over a period of 12 weeks. This trial compared placebo with 5 and 10 mg doses of solifenacin. The primary end of this study was the mean change in micturition episodes in 24 h. Changes from baseline in the mean number of urgency, nocturia and incontinence episodes, and the mean volume voided per void, were considered as secondary endpoints. Safety and tolerability were reported as secondary study objectives. These variables were based on 3 day voiding diary. 5 and 10 mg solifenacin demonstrated a significant reduction in the mean number of micturition episodes per 24 h compared to placebo: placebo, −1.59 micturitions per day; 5 mg solifenacin, −2.73 micturitions per day; and 10 mg solifenacin, −2.81 micturitions per day as shown in Fig. 27.13.

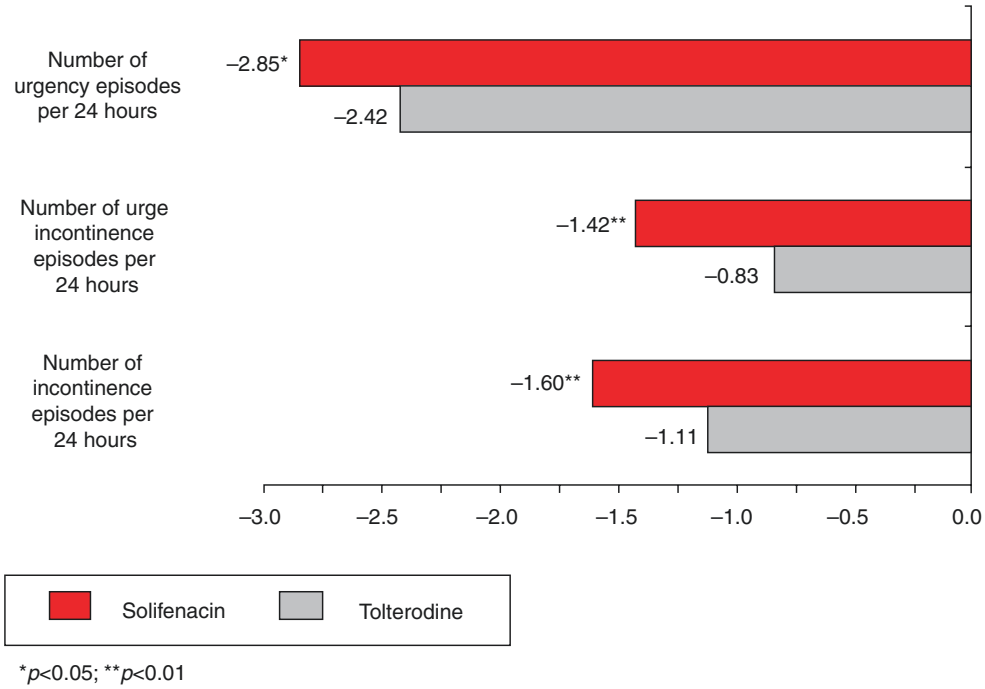

Fig. 27.11 Mean baseline to endpoint change in overactive bladder symptoms

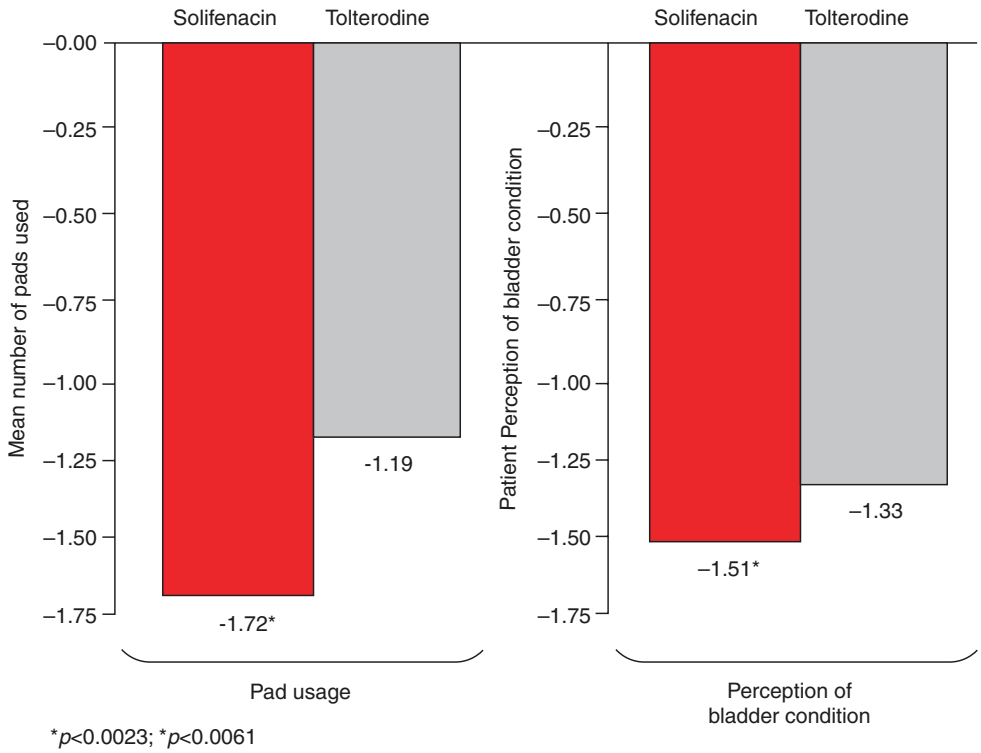

Fig. 27.12 Mean baseline to endpoint reduction in pad usage per 24 h and patient perception of bladder condition

Dry mouth was reported by 2.3%, 7.7% and 23.1% of patients receiving placebo, 5 and 10 mg solifenacin respectively. The constipation rates were placebo, 2%; 5 mg solifenacin, 3.7%, and 10 mg solifenacin, 9.1%. There was no difference in blurred vision in between placebo and solifenacin group.

Kelleher and colleagues [92] reported data on quality of life variables from two 12 weeks multicentered, double blind and randomized controlled trial in a 40 weeks open label extension of these trials. They randomized both men and women to placebo or to solifenacin in 5 mg or 10 mg doses.

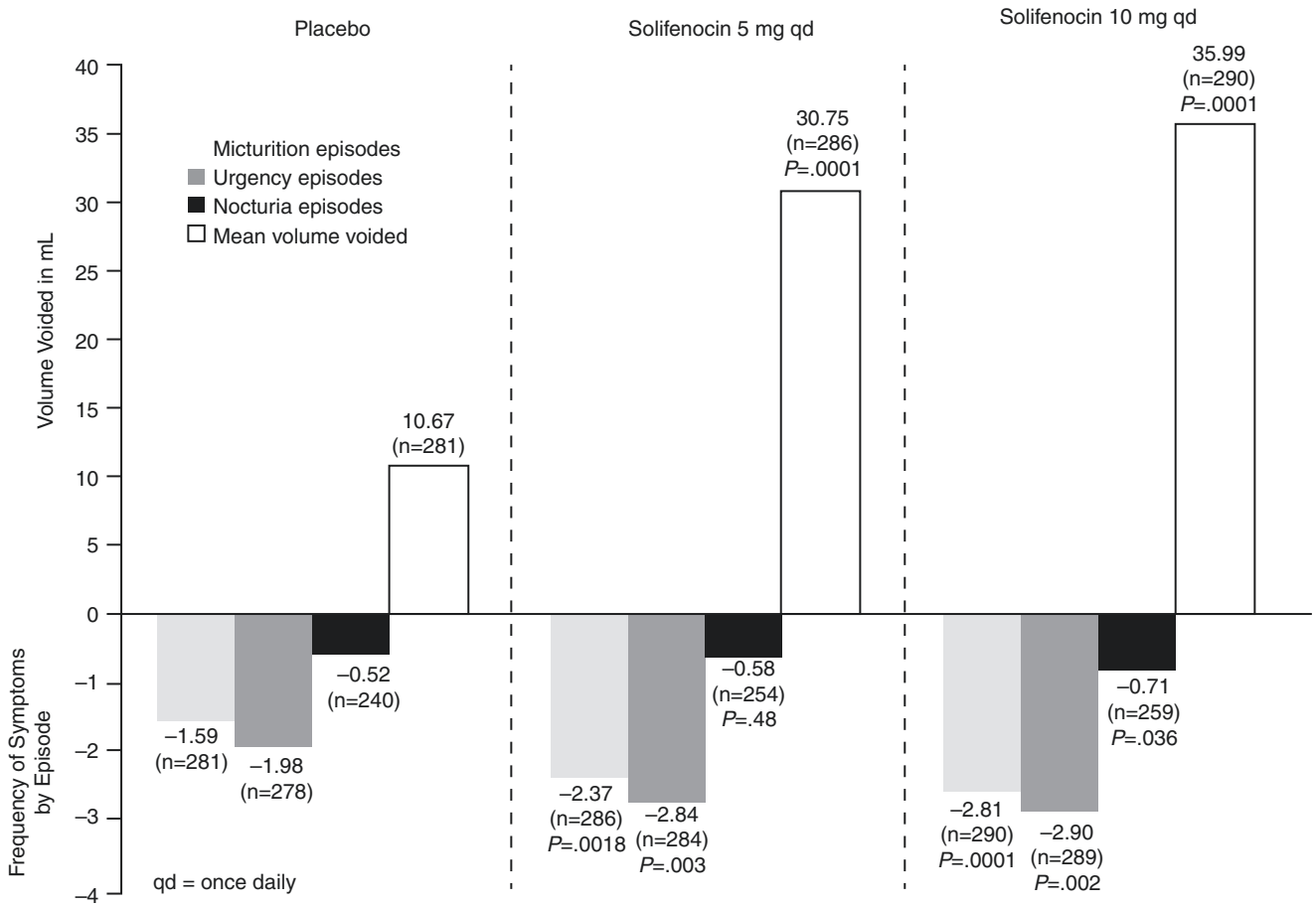

Fig. 27.13 Change in mean number of micturition, urgency and nocturia episodes per 24 h, and volume voided per micturition from baseline to end point

King's Health Questionnaire (KHQ) was used to determine quality of life among patients with lower urinary tract dysfunction. A total of 1890 patients reported quality of life data from the 12 weeks trial. The domains of the KHQ assessed general health perceptions, impact of incontinence, social and physical limitations, personal relationships, sleep/energy, emotions, severity measures, and symptom severity. Significant differences at both solifenacin doses versus placebo were observed for all domains except personal relationship after 12-week trials. Data from 40-week extension trial, solifenacin 5- and 10-mg demonstrated improvement in all quality of life domains.

Another randomized double blind controlled trial (SUNRISE) on Severity of overactive bladder symptoms and response to dose escalation conducted by Cardozo and colleagues [93] in 2013. In this 16-week clinical study, patients with severe OAB symptoms were randomized to double-blind treatment with solifenacin or placebo once daily. At 8 week, patients were allowed to increase the dose from 5 to 10 mg solifenacin and this group was entered into second randomization. Patients originally randomized to placebo continued on this treatment in a double-blind manner regardless of their dose increase request. Patients who did not request a dose increase continued for the rest of the treatment period as before. Statistically significant decrease in mean total urgency score (TUS; −2.7 vs −0.6; P = 0.010), mean maximum Patients Perception of Intensity in Urgency Scale (PPIUS) urgency rating (−0.3 vs −0.1; P = 0.034) and mean micturition frequency (−0.8 vs −0.1; P = 0.037) were observed in patients who increase their dose of solifenacin. It was concluded that increasing the dose to 10 mg solifenacin further improved OAB symptoms. Therefore, patients with severe OAB symptoms can benefit from increasing dose of solifenacin. On the other hand, more patients reported dry mouth with the 10 mg dose than with the 5 mg dose (8 [5.7%] vs 1 [0.7%]), but the absolute numbers were low and similar to or lower than previously reported rates with solifenacin. Mean change in symptoms from week 8 to end of treatment is shown in Fig. 27.14.

Summary

Solifenacin increases functional bladder capacity and reduces symptoms of urgency, frequency and incontinence. Solifenacin is highly effective and safe treatment in patients

Fig. 27.14 Mean changes in OAB variables from week 8 to end of treatment in solifenacin-treated patients who requested a dose increase at week 8

with OAB symptoms. Long term safety, efficacy, tolerability, and persistence with treatment have been established in randomized controlled trials. Moreover, dose escalation of solifenacin is not associated with higher rate of discontinuation.

27.2.1.6 Darifenacin: Overview, Effects, Side effects

Pawan Vasudeva

Overview

Darifenacin, a tertiary amine, is a selective M_3 muscarinic receptor antagonist. M_3 receptor selectivity for the drug is 9- and 12-fold greater than that for M_1 and M_5 receptor subtype, respectively, and 59-fold greater compared to both M_2 and M_4 receptor subtype.

It is supplied as its hydrobromide salt (S)-2-{1-[2-(2, 3-dihydrobenzofuran-5-yl) ethyl]-3-pyrrolidinyl}-2, 2-diphenylacetamide hydrobromide. The empirical formula is $C_{28}H_{30}N_2O_2$•HBR and it has a molecular weight of 507.5 g/mol.

Darifenacin is available in extended release (ER) formulation as a 7.5 mg/15 mg tablet. The pharmacokinetic profile of the drug is not affected by food and it can be taken with food or on an empty stomach. Mean bioavailability is 15% and 19% for the 7.5 mg and 15 mg tablets, respectively. The peak plasma concentration of darifenacin (ER) oral tablet occurs at approximately 7 h and steady-state plasma concentration is achieved after 6 days of daily dosing. It is 98% bound to plasma proteins, primarily to alpha-1-acid-glycoprotein and the estimated volume of distribution is 163 L. The drug is extensively metabolised in the liver by the cytochrome P-450 enzyme isoforms CYP2D6 and CYP3A4, the latter saturating within the therapeutic range. Only 3% of unchanged drug is excreted in urine and faeces. While dosage adjustment is not required for patients with reduced renal function, dose needs to be adjusted in patients with hepatic dysfunction (not more than 7.5 mg).Possibility of drug interactions and the need for dose adjustment must be kept in mind in patients who are concomitantly receiving other drugs that are metabolized by/influence the CYP2D6 and CYP3A4 enzymes like tricyclic antidepressants, ketoconazole, paroxetine etc. [94–96].

Effects

Darifenacin was approved for overactive bladder in 2004 and it has been extensively studied in that population. It has a well-documented beneficial effect in overactive bladder/detrusor overactivity, and tolerability and safety seems acceptable.

Unfortunately, the drug has not been studied in neurogenic bladder dysfunction. While no full text article on the role of oral darifenacin in neurogenic detrusor overactivity has been published, there is an abstract published on the subject. Carl and Laschke in their study included 38 patients of multiple sclerosis who had neurogenic detrusor overactivity with a mean residual volume of 78 cc. All patients received 15 mg of darifenacin daily for 12 weeks. The authors reported that the functional bladder capacity increased from 225 ml to 370 ml (median), compliance improved from 13 ml/cm of H_2O to 21 ml/cm of H_2O and urinary continence was achieved

in 31 patients (82%). They concluded that darifenacin suppressed urgency in vast majority of multiple sclerosis patients without an increase in residual urine [97].

Bycroft et al. have published an abstract on the role of i.v. darifenacin. They conducted a randomised, placebo-controlled, double-blind crossover study in spinal cord injured patients evaluating the role of i.v darifenacin. Eight spinal cord injured patients were recruited and were randomized to receive darifenacin 6 mg i.v. in 5% mannitol on the first or second occasion. 5% mannitol infusion without darifenacin was used for placebo. The study confirmed the efficacy of darifenacin in suppressing unstable provoked contraction secondary to neurogenic detrusor overactivity in spinal cord injured patients [98].

Side Effects

The most common side effects reported with darifenacin are dry mouth and constipation regardless of age. These are due to M_3 receptor blockade and are seen with all antimuscarinics in clinical use. They are usually not severe enough for the drug to be withdrawn or for dose to be decreased. In an open labelled 2 years extension study with 7.5 and 15 mg darifenacin per day, 23% patients reported dry mouth, of which 1.3% discontinued medication. Also, 20% patients reported constipation, of which 2.4% discontinued medication [99].

CNS Side Effects: Antimuscarinic drugs, by virtue of blocking M_1 receptors in the brain, can lead to impaired cognition, deterioration in memory, confusion and other CNS side effects. Adverse effects on CNS functioning are related to muscarinic receptor subtype selectivity and the ability of the agent to cross the blood-brain barrier, where P-gp plays a role in limiting permeability. Darifenacin is unique in the way that it is the only clinically available antimuscarinic which is a selective M_3 muscarinic receptor antagonist. Further, since it is a P-gp substrate, brain penetration is low as evidenced by preclinical studies [100]. Clinical studies have also confirmed absence of CNS side effects in both younger and elderly population. In a double-blind, four-way crossover study, 27 healthy men (aged 19–44 years) were randomized to receive darifenacin 7.5 mg or 15 mg once daily, dicyclomine 20 mg four times daily or matching placebo for 7 days. Each 7-day treatment period was separated by a 7-day washout period. The authors reported that compared with placebo, neither dose of darifenacin affected cognitive function and there was no clinically relevant effect on EEG. In contrast, dicyclomine affected cognition and also caused slowing of the EEG [101]. In another study, 150 healthy volunteers aged ≥60 years were randomized to darifenacin, oxybutynin ER or placebo in a multicentre, double-blind, double-dummy, parallel-group, 3-week study. The authors concluded that darifenacin did not have any significant effects on memory when compared to placebo. In contrast, oxybutynin ER caused significant memory deterioration [102]. Other authors have also reported that darifenacin did not affect cognition in elderly volunteers [103].

Cardiac Side Effects: Antimuscarinics, by virtue of blocking M_2 muscarinic receptors can lead to changes in the heart rate, QT interval etc. Darifenacin, being M_3 selective should logically not have any cardiac side effects and this is what clinical studies have shown. A prospective, three-way crossover, randomized, double-blind study assessed the HR effects of 7 days exposure to tolterodine (4 mg/day), darifenacin (15 mg/day) and placebo in 162 healthy participants ≥50 years (Olshansky et al.). Heart rate was measured by 24 h holter monitoring. It was found that tolterodine significantly increased HR *vs.* darifenacin (+1.84 beats/min) and HR *vs*. placebo (+1.42 beats/min), while darifenacin did not affect HR vs. placebo [104]. Darifenacin has also been shown to have no effect on QT/QT_c interval.

To summarize, while efficacy data on darifenacin in the neurogenic bladder population is limited, the drug has unique properties, especially the lack of CNS and cardiac side effects in contrast to other clinically used antimuscarinics. This could prove valuable especially in susceptible populations like elderly patients, neurological patients with cognitive defects, certain categories of cardiac patients etc. High quality clinical studies in the neurogenic bladder population are required to establish its definitive role.

27.2.1.7 Alternative Ways of Administration of Antimuscarinic Agents

Karl-Erik Andersson

Transdermal Way

Transdermal Oxybutynin (OXY-TDS)

Transdermal delivery alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [105] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). Dmochowski et al. [106] analyzing the combined results of two RCTs concluded that transdermal oxybutynin was shown to be efficacious and well tolerated. The most common systemic side effect was dry mouth (7.0% vs placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1%. Cartwright and Cardozo [107], reviewing published and presented data concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics – however, this benefit was offset by the rate of local skin reaction. The reviews of Sahai et al. [108] and Staskin and Salvatore [109] largely confirmed

these conclusions, which also have been supported by further studies [110]. Recently the transdermal patch (3.9 mg/day) has been shown to be subjectively effective in a small paediatric population, but with 35% skin site irritation and 20% discontinuation rate [111].

Oxybutynin Topical Gel

Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. Oxybutynin topical gel (OTG) was approved by the US FDA in January 2009. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area [112]. The 1 g application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and a "favorable" N-desethyloxybutynin metabolite: oxybutynin ratio believed to minimizing antimuscarinic side effects [113]. In a multicenter RCT, 789 patients (89% women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks [112]. The mean number of urgency episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm ($P < 0.0001$). Urinary frequency decreased by 2.7 episodes per day and voided volume increased by 21 mL (versus 2.0 episodes [$P = 0.0017$] and 3.8 mL [$P = 0.0018$], respectively, in the placebo group). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. It was felt that improved skin tolerability of the gel over the OXY transdermal patch delivery system was secondary to lack of adhesive and skin occlusion. The gel dries rapidly upon application and leaves no residue; person-to-person transference via skin contact is largely eliminated if clothing is worn over the application site [114]. The evolution of the transdermal gel allows greater patient tolerability and improved compliance. This was confirmed by Sand et al. [115] showing that in 704 women with OAB OTG significantly reduced the number (mean ± standard deviation) of daily incontinence episodes (OTG, −3.0 ± 2.8 episodes; placebo, −2.5 ± 3.0 episodes), reduced urinary frequency, increased voided volume, and improved select health-related quality-of-life domains vs placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%).

Intravesical Way

One way to reduce adverse effects is intravesical administration. In patients with NDO, intravesical *atropine* may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [19]. It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO [116]. In children, With NLUTD, intravesical *oxybutynin* has been evaluated for its potential to decrease the side effects by reducing first pass metabolism in the liver while maintaining high systemic efficacy and bioavailability [19]. A 15-year mean follow-up following transition from oral to intravesical oxybutynin for pediatric NLUTD in ten children with DSD demonstrated ongoing suppression of DO, maintenance of long-term effects on bladder compliance and increased bladder capacity (from 5th to 50th percentile for age). Intravesical oxybutynin was well-tolerated; no side effects were reported [117].

Intravesical application of *trospium* may be an interesting alternative. Frölich et al. [118] performed a randomised, single-blind, placebo-controlled, mono-centre clinical trial in 84 patients with urgency or urgency incontinence. Compared to placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed [119], thus offering an opportunity for treatment with minimal systemic antimuscuscarinic effects.

27.2.1.8 Phosphodiesterase (PDE) Inhibitors

Karl-Erik Andersson

Pharmacology

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. There is *in vitro* evidence that PDE5 inhibition might relax the smooth muscle of the prostate, bladder, and urethra, dilate the pelvic vasculature (including the microvasculature), and modulate sensory bladder functions [120–122]. Systemic vardenafil reduced both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord injury rats, indicating potential mechanisms by which PDE5-Is improve storage symptoms in SCI patients [123]. The effect of vardenafil on OAB-symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (SHR) [124]. Improvement of bladder blood flow to the LUT has been suggested [122], and this has been supported by studies in animals with chronic bladder ischemia [125]. However, Pinggera et al., using transrectal ultrasonography, compared the effects of tadalafil 5 mg/day and placebo given for 8 weeks to men with moderate to severe LUTS/BPH. They found no differences between the treatments, but did not exclude that changes in blood flow may have occurred which for several reasons could not be detected.

Efficacy and Side Effects

Several randomized, placebo-controlled clinical trials have demonstrated that daily treatment with 5 mg tadalafil

improves safely BPH-related LUTS [19, 126–129]. A number of RCTs are available comparing the combination of α-AR antagonists and PDE5 inhibitors vs α-AR antagonists alone [130]. In these studies, different PDE5 inhibitors and different doses were administered. PDE5-inhibitors significantly improve IPSS and IIEF scores, but not Qmax when compared to placebo. According to a meta-analysis by Gacci and co-workers, differences in IPSS score were significantly lower in older and obese patients [131]. The combination of PDE5-inhibitors and α-AR-blockers lead to significant improvements of the IPSS and IIEF score as well as Qmax when compared to the use of α-AR-blockers alone. Dmochowski showed that tadalafil once daily for LUTS had no significant effect on bladder function as measured by detrusor pressure at maximum urinary flow rate or such as maximum detrusor pressure and bladder outlet obstruction index while improving IPSS [132]. PDE5-inhibitors were generally shown to be safe and well tolerated. The most common adverse effects of tadalafil in the treatment of LUTS are mild to moderate dyspepsia and flushing, with a low rate (2–4%) of discontinuation.

Currently, tadalafil is the only FDA approved PDE-5 inhibitor for treatment of male LUTS.

27.2.1.9 Beta Adrenoceptor Agonists (Mirabegron): Overview, Effects and Side Effects

Yasuhiko Igawa

Background

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced relaxant effect [133]. In late 1970s, functional characteristics of the β-ARs of the human bladder were proposed to be typical of neither β1-, nor β2-ARs [134, 135]. In 1989, a third subtype, β3-ARs was isolated and cloned [136]. β3-ARs are widely distributed in the body, including adipose tissue, the heart and vascular system, and the bladder, although distribution is highly species dependent [137]. All three β-AR subtypes (β1, β2 and β3) were identified in the human detrusor [138–140], as well as in the human urothelium [141]. Real-time reverse transcription-polymerase chain reaction revealed predominant expression of β3-AR mRNA in the human detrusor muscle [142]. The preclinical functional evidence for an important role of β3-ARs in normal and neurogenic bladders is convincing [137–140, 143, 144]. However, the human detrusor also contains β2-ARs and most probably these two receptors are involved in the physiological effects (relaxation) of noradrenaline on human detrusor [76, 137, 144, 145].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species, is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K+ channels, particularly BKCa channels, may be more important in β-AR-mediated relaxation than cAMP [146–149].

It has been generally considered that β3-AR agonists can relieve overactive bladder (OAB) symptoms by relaxing detrusor muscle, inhibiting spontaneous contractile activity in the detrusor (*in vitro:* microcontractions*; in vivo*: non-voiding contractions), and reducing bladder afferent activity [137, 150–155].

In addition, β3-AR agonists may down-regulate acetylcholine (ACh) release by activation of pre-junctional inhibitory β3-ARs resulting in an inhibitory control of parasympathetic activity, which may be of importance assuming that acetylcholine (ACh) release from cholinergic nerve terminals during bladder filling contributes to OAB symptoms [156, 157]. It has been shown that activation of β-AR by isoproterenol in rat urothelial cells can release nitric oxide (NO) through an increase in intracellular Ca2+ by cAMP accumulation [158]. Activation of urothelial β-AR releases not only NO but also a urothelial-derived factor (UDRF) that inhibits contractions induced by carbachol in the pig detrusor [159]. The β-AR involved in the release of UDIF was determined to be a β3-subtype [160]. A similar UDIF released by β-AR activation in the human bladder urothelium is reported to inhibit the β-AR agonist-induced relaxation of the human detrusor smooth muscle [161]. However, to what extent a urothelial signaling pathway contributes *in vitro* and *in vivo* to the relaxant effects of β-AR agonists in general, and β3-AR agonists specifically, remains to be elucidated.

The *in vivo* effects of β3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [137, 140, 144, 161–164]. Although a number of β3-AR selective agonists are currently being evaluated as potential treatment for OAB, so far the only drug approved for treatment in humans is mirabegron.

Mirabegron

Pharmacokinetics

Mirabegron is highly lipophilic and rapidly absorbed after oral administration. The time to maximum plasma concentration (T_{max}) is about 2 h and the terminal elimination half-life ($t_{1/2}$) is approximately 23–25 h [165, 166]. Clinically, mirabegron is administered as an extended release tablet (Oral Controlled Absorption System; OCAS).

The drug circulates in the plasma as unchanged active compound and as inactive metabolites. Most of an administered dose is excreted in urine, mainly as the unchanged form, and one third is recovered in feces, almost entirely as

the unchanged form [167]. It is not known if the drug secreted in the urine will have any effect on bladder function. Theoretically, the drug should be able to pass the blood–brain barrier, but information on possible CNS effects of mirabegron and other β3-AR agonists are scarce [168]. Mirabegron is metabolized in the liver via multiple pathways, mainly by cytochrome P450, CYP3A4 and CYP2D6 [169, 170], creating a risk for drug–drug interactions.

Clinical Efficacy and Safety for Overactive Bladder Patients

The effects of mirabegron in men and women with OAB have been summarized in several recent reviews [171–173], and also in men with both voiding and OAB symptoms [174, 175]. Mirabegron has a documented beneficial effect in the treatment of OAB/DO, and seems to have an acceptable side effect profile. Mirabegron seems to have definite advantages over the antimuscarinics with respect to adverse events. Dry mouth and constipation are essentially non-existent in comparison to placebo [171–173].

To achieve maximal reduction in OAB symptoms, it was postulated whether a β3-AR agonist in combination with an antimuscarinic would be beneficial. A phase II, multicenter, double-blind study randomized 1306 participants to one of 12 groups: solifenacin or mirabegron alone in varying doses, combinations of both at different doses, and placebo [176]. Compared to the improvement in OAB parameters from baseline with solifenacin 5 mg there were statistically significant improvements with all combinations except solifenacin 2.5 mg plus mirabegron 25 mg. The adverse effects classically associated with antimuscarinic use were no more severe in the combination treatments, as they were in the corresponding dose of solifenacin monotherapy. These data are promising and reflective of an already common clinical practice.

Clinical Efficacy for Neurogenic Detrusor Overactivity and Low Compliance Bladder

There are few studies on the efficacy of mirabegron for either neurogenic detrusor overactivity (NDO) or low compliance bladder.

Wöllner and Pannek [177] recently reported that 15 patients with NDO treated with mirabegron for a period of at least 6 weeks, showed significant reduction of the frequency of bladder evacuation per 24 h (8.1 vs 6.4, P = 0.003), and of incontinence episodes per 24 h (2.9 vs 1.3, P = 0.027). Furthermore, urodynamic studies revealed improvements in bladder capacity (from 365 to 419 ml), compliance (from 28 to 45 ml/cm H_2O) and detrusor pressure during storage phase (45.8 vs 30 cm H_2O). At follow-up, 9/15 patients were satisfied with the therapy.

Wada et al. [178] retrospectively examined the efficacy of combination therapy with mirabegron in seven patients (five men and two women) with NDO or low compliance bladder (<10 ml/cmH_2O) refractory to anti-cholinergic treatment. Underlying diseases were spinal cord injury in three patients, spina bifida in two, spinal cord infarction in one, and post-radical hysterectomy in one. After mirabegron, urinary incontinence was improved in all patients. G3 bladder deformity was improved to G2 and G1 in one patient each, and vesicoureteral reflux (VUR) disappeared in all three patients. DO disappeared in two of the five patients, and bladder compliance was improved in all four patients with low compliance bladder.

Kamei et al. [179] investigated video-urodynamic effects of mirabegron in nine patients (three men and six women, age 17–68 years) with low-compliance bladder including seven patients with neurological diseases (three spinal cord injury, four myelomeningocele, and one post-radical hysterectomy). Mirabegron treatment significantly increased first desire to void and cystometric capacity with an average increment of 80 mL (P = 0.027) and 123 mL (P = 0.005), respectively. Bladder compliance also significantly increased (mean value 8.1 mL/cmH_2O before, 18.2 mL/cmH_2O after, P = 0.024). In the six patients who had been taking anticholinergic agents at baseline video-urodynamic study and then switched to mirabegron, mean cystometric capacity and bladder compliance were also increased significantly from 208.3 to 346.8 mL (P = 0.015) and from 7.2 to 17.5 mL/cmH_2O (P = 0.047), respectively. VUR grade was improved in three of the four patients who had shown VUR on cystography before treatment.

Due to the limited number of patients and the retrospective nature of these studies, prospective, placebo-controlled studies are required to confirm the beneficial effects of mirabegron on NDO and low compliance bladder suggested by these studies.

New Developments

Thiagamoorthy et al. [180, 181] reviewed "novel and putative" β3-AR agonists for management of OAB, including solabegron, ritobegron, TRK-380, AJ-9677, BRL37344, and CL-316243. There seems to be a number of β3-AR agonists in the pipeline some of which are under development. However, it is uncertain which, if any, will come to market and be available for the management of OAB.

Solabegron

Solabegron (GW427353) is a selective β3-AR agonist developed with the aim of treating OAB and irritable bowel syndrome [163]. In a phase II multicenter, randomized, proof-of-concept trial in 258 women with wet OAB. The drug produced a statistically significant difference in percent change from baseline to week 8 in incontinence episodes over 24 h (primary outcome) when compared with placebo (p = 0.025) and was well tolerated [182].

Ritobegron

In its first phase III study, compared to placebo, ritobegron did not significantly improve the mean number of micturitions per 24 h. A long-term safety and efficacy study was subsequently withdrawn, and ritobegron does not seem to have been developed further [180, 181].

Vibegron

An early-generation clinical β3-AR agonist MK-0634 exhibited efficacy in humans for the treatment of OAB, but development was discontinued due to unacceptable structure-based toxicity in preclinical species. Vibegron (MK-4618, KRP-114V), was claimed to have an overall superior preclinical profile compared to MK-0634 [183]. Vibegron is a potent, selective full β_3AR agonist across species, and it dose-dependently increased bladder capacity, decreased micturition pressure, and increased bladder compliance in rhesus monkeys. The relaxation effect of vibegron was enhanced when combined with muscarinic antagonists, but differentially influenced by muscarinic receptor subtype selectivity [184]. Its phase III studies for the treatment of OAB have been progressing.

27.3 Drugs Decreasing Bladder Outlet Resistance

Karl-Erik Andersson

27.3.1 Alpha-Adrenoceptor Blockers: Overview, Effects and Side Effects

Subtype selective and non-subtype selective α_1-adrenoceptor (AR) antagonists have been partially successful in decreasing bladder-outlet resistance, residual urine, and autonomic dysreflexia in patients with [185, 186]. These drugs have long been a mainstay in the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH). The α_1-ARs are the main subtype located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra and mediates contraction of the smooth muscle in these tissues [187]. α_1-AR antagonists are believed to act by relaxing the smooth muscle component of the outflow region allowing for better urine flow, which relieves emptying symptoms. However, this mechanism does not explain why men also can get immediate relief of their lower urinary tract storage symptoms. The weak correlation between LUTS and prostatic enlargement, outflow obstruction, or both, however, has refocused interest on the role of extra-prostatic α_1-ARs both in the pathogenesis of LUTS and their treatment.

Moon et al. [188] studied 82 patients with neurogenic bladder with silodosin (8 mg/day) and found that after 12-weeks of treatment, mean total international prostate symptom score decreased significantly from 22.23 ± 6.80 to 14.98 ± 9.48. Voiding symptoms and storage symptoms were also improved by decreasing in international prostate symptom score-QoL from 4.62 ± 0.92 to 3.48 ± 1.63. Maximum flow rate increased significantly from 10.72 ± 2.66 to 15.14 ± 6.63. The main adverse event was ejaculation disorder, but no serious adverse events related to silodosin were noted. Previous studies with other α_1-AR antagonist also report beneficial effects. In 12 SCI patients with high bladder storage pressures and poor compliance terazosin 5 mg daily administered for 4 weeks, decreased detrusor pressure at maximum capacity with a mean of 36 cmH_2O, and improved compliance (73%) compared to baseline [189]. In a placebo controlled double blind trial with 136 patients with neurogenic bladder patients given placebo or 30 or 60 mg of urapidil for 4 weeks, Yasuda et al. [190] showed a statistically significant decrease in urodynamic DO in. the highest dose group. O'Riordan et al. [191] performed a randomized placebo controlled study on 40 men with multiple sclerosis using indoramin. They found a mean 41% improvement in peak flow rate in the indoramine group compared with a 7.4% deterioration in the placebo group. Residual volume improved in both groups, and the patients taking indoramin reported a greater improvement in urinary symptoms than those treated with placebo. Studies with tamsulosin [185, 192] have shown improvements in selected patients with neurogenic bladder.

Abrams et al. [185] performed a 4-week RCT of 263 patients with suprasacral SCI followed by a 1-year open label study of placebo compared to tamsulosin. Maximum urethral pressure (MUP), which was the primary outcome of the study, was not significantly different between groups at 4 weeks. However, in the 186 patients who completed the 1-year open label study there were significant improvements in MUP (−18 cmH_2O) as well as improved maximum cystometric capacity, post void residual and voiding time.

α_1-AR antagonists (e.g., prazosin, terazosin, tamsulosin therapy has also been shown to improve autonomic dysreflexia symptoms in patients with SCI [185, 193–195].

Reported side effects of α_1-AR antagonists include nasal congestion, abnormal ejaculation (especially with tamsulosin), fatigue, headache, dizziness, postural hypotension, syncope, and intraoperative floppy iris syndrome [196, 197]. A meta-analysis revealed that alfuzosin, terazosin, and doxazosin, and doxazosin GITS showed a statistically significant increased risk of developing vascular-related events compared with placebo, whereas tamsulosin showed a numerical increase that was not statistically significant [196]. Silodosin appears to have less cardiovascular side effects [197].

27.3.2 Skeletal Muscle Relaxant Agents (Baclofen): Overview, Effects and Side Effects

Baclofen. Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex in several points along its central pathway [198]. As an agonist on GABA(B) receptors, *baclofen* was used orally in patients with idiopathic detrusor overactivity. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [199].

Baclofen is one of the most effective drugs for the treatment of spasticity following spinal cord injury, traumatic or hypoxic brain injury, and cerebral palsy [200], and *intrathecal* baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [201]. In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

27.4 Antidiuretic Hormone (ADH: Desmopressin): Overview, Effects and Side Effects

Karl-Erik Andersson

27.4.1 Pharmacology

The endogenous hormone vasopressin (also known as antidiuretic hormone) has two main functions: it causes contraction of vascular smooth muscle and stimulates water reabsorption in the renal medulla. These functions are mediated by two specific vasopressin receptors of which there are two major subtypes, the V_1 and V_2 receptors. The V_2 subtype is particularly important for the anti-diuretic effects of vasopressin. Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for anti-diuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and nasal administration. It has a fast onset of action, with urine production decreasing within 30 min of oral administration]. An oral lyophilisate (MELT) formulation requiring no concomitant fluid intake is currently available.

27.4.2 Efficacy and Side Effects

The clinical efficacy of desmopressin for treatment of nocturnal polyuria is well documented in non-neurogenic patients [19]. There are several studies showing efficacy also in NBD.

Spinal cord injured patients often have high urine output at night, particularly those with higher level lesions [202]. The nocturnal polyuria is multifactorial with fluid retention during the day secondary to their autonomic dysfunction, lack of ambulation, and arginine vasopressin production disorders [203]. Several small studies have addressed this problem in the SCI and spina bifida population. Desmopressin was used to treat patients with pediatric neural tube closure defect with daytime continence but persistent bedwetting in two studies [204, 205]. Combining their results 81.4% (35/43) of patients became totally dry and 88.4% (38/43) were significantly improved. The majority of "failures" in these studies were patients who discontinued treatment. There were no adverse events noted in either study. Two small studies have assessed desmopressin in patients with SCI and nocturnal polyuria [203, 206]. Combining their results 11/15 patients eliminated the need for CIC at night with the use of desmopressin before bed and the remaining four patients were reduced to only one catheterization during the night. Again, no patients suffered significant side effects such as hyponatremia or fluid overload and only two patients had transient headaches. The use of desmopressin to treat nocturia in MS has been better studied. A meta-analysis combining results from five randomized double-blind placebo controlled crossover studies had 98 patients available for analysis [207]. All studies showed a statistical reduction in voided volume for 6-h following administration of desmopressin. None of the studies reported a significant reduction in serum sodium, 0–8% of patients reported symptoms of fluid retention and 3–4% of patients reported transient headache. In one study [208] 82% of patients requested continuation of the drug after the trial and patients reported that the medication improved their sleep which in turn improved their quality of life. The original intranasal spray that was studied in most of these trials is no longer available, but has been replaced with tablet forms. All patients need a baseline serum creatinine to ensure good renal function and a baseline sodium level before starting therapy. Patients can be started at 0.1 mg every night at bedtime (QHS) or 0.2 mg QHS with lower doses use in the elderly and female patients. Serum sodium should be repeated within a week and the dose can be escalated provided there is no hyponatremia or adverse events. Blood work needs to be repeated with every dose escalation and yearly thereafter. Hyponatremia is the most feared side effect of this class of medications that can present with confusion, hallucinations or in severe cases seizure.

27.5 Agents Increasing Detrusor Contractility(Cholinergic Drugs)

Karl-Erik Andersson

Muscarinic receptor agonists and cholinesterase inhibitors. It is well established the acetylcholine is the main

contractile transmitter in the detrusor muscle, and that release of this agent induced by activation of the parasympathetic outflow from the spinal cord leads to a co-ordinated bladder contraction and bladder emptying with simultaneous relaxation of the outflow region [209].

Standard pharmacotherapy of impaired bladder emptying has for a long time included muscarinic receptor agonists, such as bethanechol and carbachol to directly stimulate muscarinic receptors on the detrusor muscle, or choline esterase inhibitors, like distigmine to reduce the degradation of acetylcholine Andersson et al. [19]. However, based on available information it has been considered that little, if any, beneficial effects can be obtained in preventing or treating emptying difficulties [19, 210]. One of the reasons why these drugs do not work is that direct stimulation of detrusor muscarinic receptors will cause contraction (contracture) of the bladder without simultaneous relaxation of the outflow region. Systemic administration of a muscarinic receptor agonist has no selectivity for the bladder which means that action on non-target sites will cause adverse effects. Both bethanechol and carbachol have low oral bioavailability which makes it difficult to attain "active" blood concentrations.

27.6 Increasing Bladder Outlet Resistance Agents

Karl-Erik Andersson

27.6.1 α-Adrenoceptor Agonists

Several drugs with agonistic effects on peripheral α-ARs have been used in the treatment of SUI. Ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [19]. A Cochrane review [211] assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women. The authors concluded, "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of pad changes and incontinence episodes, as well as, improving subjective symptoms". Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [76]. Midodrine and methoxamine stimulate α_1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate at best, and the clinical usefulness seems to be limited by adverse effects [211].

27.6.2 Duloxetine

Duloxetine hydrochloride is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 h [212].

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation. The mechanisms of action and the physiologic effects of duloxetine has been discussed in detail by Thor et al. [213].

The clinical efficacy in stress urinary incontinence (SUI) in women has been well documented in a number of studies [19]. However, reports of use of the drug with specific reference to patients with NBD seem scarce. Hurley et al. [214] characterized the safety of duloxetine for treatment of SUI in women, using an integrated database generated from four published placebo-controlled clinical trials. The database included 1913 women randomized to duloxetine (N = 958) or placebo (N = 955), examining adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiograms, and laboratory analytes. AEs occurring initially or worsening during the double-blind treatment period were considered treatment-emergent (TEAE). Differences between duloxetine-treated and placebo-treated groups were compared statistically. Common TEAEs included: nausea (23.2%), dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%), and diarrhea (5.1%). Most TEAEs that emerged early were mild to moderate, rarely worsened, and resolved quickly. Overall AE discontinuation rates were 20.5% for duloxetine and 3.9% for placebo ($P < 0.001$). Most discontinuations (83%) occurred within the first month of treatment.

Persistence on duloxetine was studied by Vella et al. [215] who found that only 31% of an original cohort of 228 were still taking drug beyond 4 weeks, 12% at 4 months, 10% at 6 months, and 9% at 1 year. Fifty-six percent of the discontinuations were attributed to side effects, 33% to lack of efficacy. Bump et al. [216], however, reported that the positive effects of duloxetine were maintained in patients who continued treatment up to 30 months, but admitted that this subgroup was likely to include predominantly patients who had favorable responses. The number decreased from 1424 in this cohort at 3 months to 368 at 30 months.

27.7 Combination of Drugs with Different Mechanisms of Action

Karl-Erik Andersson

A number of studies have demonstrated the superior efficacy of combination treatment with an α_1-AR antagonist and an antimuscarinic for alleviating symptoms of benign prostatic hyperplasia (BPH) and concomitant OAB compared to either monotherapy [19]. However, there are studies suggesting that this is also valid for NDO. In a clinical study of 12 individuals with SCI who had poor bladder compliance despite taking an antimuscarinic and performing CIC, the addition of 5 mg of terazosin for 1 month significantly improved their bladder capacity, pressures and compliance. Interestingly, these urodynamic improvements disappeared after stopping the alpha blocker indicating the reversibility of their action [189]. Other combination therapies that have been successful and safely utilized include tricyclic antidepressants in combination with anticholinergics in children with nocturnal enuresis which was resistant to tricyclic antidepressants (TCAs) alone [217]. Two independent studies have reported their results in treating individuals with refractory incontinence or poor compliance due to NGB with triple drug therapy consisting of an antimuscarinic combined with an alpha blocker and imipramine [130, 218] In this group of individuals who were refractory to antimuscarinics alone, maximum detrusor pressure, capacity and bladder compliance were all improved as well as the resolution of subjective patient incontinence. Side effects were tolerable and the most common were dry mouth and constipation.

Several clinical trials have demonstrated the efficacy and safety of the combination therapy of antimuscarinics and β_3-AR agonists in patients with OAB [219, 220]. However, published experiences with this combination in patients with NDO seem scarce.

27.8 Conclusions and Recommendations on Drug Treatments

The lower urinary tract (LUT) in health is regulated by coordinated multi-level neurological inputs which require an intact central and peripheral nervous system. Neurogenic LUT dysfunction (NLUTD) is a common result of neurological disease and the patterns of bladder storage and voiding dysfunction depend upon the level of neurological injury. Since neurological lesions and resulting NLUTD are individually different, a management strategy tailored for each patient is required. There are many different combinations of detrusor and sphincter dysfunction, and a personalized diagnosis is mandatory, and will guide the choice of drug therapy. Neurogenic detrusor overactivity (NDO) is a common, but treatable condition. Antimuscarinics are first line treatment for patients with NDO and poor compliance.

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External Appliances

28

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28.1 Indications for Male External Catheter (MEC)

A MEC is indicated in male patient if other curative treatment options have either failed or are deemed unsuitable, perhaps on account of a patient being unfit for any other intervention or are requested by the patient. The usual scenarios are urinary incontinence without significant post-void residual urine, overactive bladder with urge UI and significant post-void residual urine in patients that are incapable or unwilling to perform IC or other treatment options, but without other complications of chronic urinary retention.

MEC can be used in men with stress urinary continence when further interventions, e.g. male sling or artificial urethral sphincter, are not suitable or unacceptable to the patient.

28.2 UI in Men with Neurological Disorders and Neuromuscular Syndromes

Male patients with poor mobility, dementia, impaired cognition or impaired vision, or for whom accessing a toilet poses a safety issue. For some of these patients, a social support or family network should be available to ensure that the MEC is used both appropriately and effectively with regular review to ensure its continued use is in the patient's best interests.

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28.3 Contraindications for MEC

An absolute contraindication is the known presence of high pressure chronic retention which may be the underlying causative pathology of UI. Relative contraindications are more reflective of the fact that most clinical scenarios like low pressure chronic retention or bladder acontractility are better managed with alternative means, e.g. long term intermittent/indwelling catheterisation.

Other limiting and relative contraindications for the use of MEC include dermatological issues such as excoriated penile skin, psoriasis and localised allergy to materials used as well as cognitive impairment, physical inability to apply the device or perhaps visualise the penis thus hindering adequate application, patients with a high BMI are at greater risk of this because of blocked vision due to abdominal girth, a prominent supra public fat pad and accessible penile length upon which to place the MEC.

28.4 Male External Catheter

A male external catheter (MEC) is used for the management of urinary incontinence in men. The device is a simple sheath that is placed over the penis in the same way as a condom. However, unlike a normal condom, a MEC has a drainage tube that allows urine to pass into a storage bag fastened around the leg. The MEC is a non-invasive device [1].

Synonyms for MEC are: condom catheter, condom drainage system, penile sheath, external catheter, urine collection device, condom urinal, urisheath, amongst patients also known as Texas Condom. The most commonly used term used for this device is "male external catheter" [2].

28.4.1 Products and Materials

There are various products available for the management of urinary incontinence. It is important that healthcare

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_28

professionals know both, products and application techniques, before applying it [1, 3].

28.4.1.1 Types of Adhesives Used to Attach MECs to the Penis Shaft [1, 4]

(a) Self-adhesive MEC (one-piece system): this ready-to-use condom has a sticky film on its inner surface which attaches the condom to the penis. It can be rolled up and fixed in place. There are variations among the different types of adhesives, the location where the adhesive is positioned on the MEC, as well as how large the adhesive area is. The size of these parts differs between companies and various products.
(b) Adhesive strips: Some MECs require a double-sided adhesive strip to attach them to the penis. The adhesive strips are placed on the penis (almost encircling it spirally) and the MEC is rolled over the penis, attaching to these adhesive strips.
(c) Skin adhesives (spray and paste): Non-adhesive MECs do not contain an adhesive film, so they require application of skin glue onto the skin before rolling it over the penis.

28.4.1.2 Materials

(a) Silicone: Allergic reactions with silicone are rare. Its "skin-friendliness" is a great advantage. Moreover, the translucent material provides a view on the skin that allows one to recognize irritation or other skin problems.
(b) Latex: Some patients may have or have developed latex sensitivities and develop an allergic reaction. For this reason, in several European countries the use of latex products in the medical environment is fading off.
(c) Polyvinyl chloride (PVS): The production of PVC requires the incorporation of plasticizers to soften the material. Such "softeners" may be hazardous in long-term use, which should be taken into consideration when deciding to use PVC products long-term.
(d) Polyurethane (PU): It is a synthetic material and many latex-free MECs are made from PU. PU MECs are thinner than other types. This results in improved wearer comfort compared to other materials.

28.4.1.3 MECs with Special Features

There are MEC that contain an anti-reflux valve (inner flip) to prevent urine backflow and leakage. There are also MECs on the market with an applicator or special help stripes to improve handling. The loop of the help stripe can be pulled which makes rolling out the MEC easier. Some MECs also comprise anti-kinking/twisting features intended to improve drainage by reducing kinking and twisting at the distal end, near the connection to the drainage bag tube [5].

MECs have the advantage of diverting the urine to a bag thus decreasing urine odor and protecting the skin from contact with urine. In patients with fecal incontinence, especially in the presence of liquid stool, the condom catheter is protecting the urinary tract from stool [6, 7].

28.4.2 Assessment

In order to select the proper device the patient's individual situations as well as the measures of the penis have to be considered.

28.4.2.1 Patient's Situation

Each patient should be assessed individually as there is no single product that fits all. Patients must have sufficient penile length and girth. There is a definite need for compliance when using MECs, therefore both, patient and carer, need to discuss the issue before a decision is finally made [2].

The objective for fitting a MEC is to maximize the user's quality of life [7]. In regards to the patient's situation one should be sure that the MEC is the most appropriate management choice and will not result in problems.

28.4.2.2 Measuring

To find the appropriate size the MEC, the circumference of the penis needs to be measured. The penis should be measured at the shaft where its diameter is largest in order to assess the correct size. Moreover, also erections have to be taken into consideration in order to avoid compressive damage [8].

During measurement, the patient should be seated on a chair or on the edge of a bed with the legs slightly spread. In this position both, the scrotum and penis, are in their natural anatomic orientation and the penis can be measured best. If the size turns out to be between two sizes, patients should try both sizes at home. MEC materials are sufficiently flexible and allow a snug, but not tight fit. Many manufacturers offer sizing guides (e.g. cardboard molds or patterns) to find the size which is safe and comfortable. One must know that the manufacturer sizes may vary and sizing guides provided by one manufacturer should not be used for another product [2, 9].

It is more important to determine the exact diameter of the penis rather than the length of the penis. Some products have different lengths so the optimal size and length can be selected.

28.4.2.3 Retracted Penis

Penile retraction occurs when the penis retracts inside the prepubic fat. This is a common occurrence in older men. Special MECs are available on the market for patients with a shorter or retracted penis. Since a retracted MEC is shorter in length than a regular MEC, there is less area for the adhesive

side of the catheter. Therefore, it is most important that the correct male external catheter size is selected. To apply the MEC, the patient should lie on his side. In this position, it is easier to reach most of the penis to attach the MEC. When the MEC is placed in the correct way, it can "handle" a retraction of the penis better [1, 10].

In selected patients with a short/retracted penis the implantation of a penile prosthesis may be the solution.

28.4.3 Selection

28.4.3.1 One- or Two-Piece MEC

Most patients prefer a one-piece system. However, a two-piece MEC can be beneficial for those patients, of whom the glans is larger than the shaft of the penis or if the patient has developed a sensitivity to the adhesives used in the one-piece systems.

28.4.3.2 The Drainage Bag

There are different sizes of bags. A patient might use a smaller bag during the day and a larger one at night, preferably one which can be connected to a night-urine bag.

The leg bag can be placed at different positions on the leg: thigh, knee and under the knee. A leg bag is the best choice for ambulatory patients.

Urine bags should be changed at least once weekly, however, in many institutions the bag is changed each time that the MEC is changed.

In case of impairment of hand function or vision, the type of tap can be an important factor for patients to be as independent as possible when emptying the bag.

28.4.4 Application of the MEC

The skin should be dry and undamaged before placing the MEC onto the penis. If the skin is undamaged, normal personal hygiene is sufficient. Hair should be trimmed if necessary to prevent it being caught in the sheath. Alternatively a hole can be torn in a tissue then placed over the penis to push the hair back [1].

28.4.5 Skin Care and Meatal Cleansing

Special skin care products are not necessary. They can interfere with the adhesiveness of the condom and can irritate the skin. Any skin lesion has to be observed daily. A clean non-occlusive wound-dressing can be placed over the affected area. Special attention has to payed in patients with sensory deficits that may not be aware that the condom is too tight [8].

28.4.6 Observation of the Applied MEC

Adequate products, the correct application technique and right size prevent leakage. With large volume urine losses a MEC with an anti-reflux membrane can provide the integrity of the adhesive, thus protecting against leakage.

Avoid kinking or twisting of the sheath or the drainage bag which can cause the urine to pool, with the consequence of weakening the adhesive or blocking drainage completely [1].

28.4.7 Removing the MEC

Removing the MEC is achieved by rolling the condom off. Usually the adhesive comes off the skin, if something remains it can be washed off with skin care products or rubbed off gently. Water and soap are recommended.

It is of paramount importance that the patient is educated how to use his MEC.

28.4.8 Complications

In a study of men with SCI complications related to improper use of MECs are reported in 15%. The risk of complications is large in patients with spinal cord injury because of decreased sensation and atrophic changes of the skin [11].

28.4.8.1 Urinary Tract Infection

Results of studies deciding if the risk of UTI is lower in men using MECs compared to indwelling catheters are controversial. It is estimated that the incidence of UTI is 40% in MEC users. Saint [14] found that the use of MECs is less likely to lead to bacteriuria, symptomatic UTI, or death than the use of indwelling catheters in non-demented men [10]. Urine from MEC users had fewer biofilm-forming bacteria than urine from indwelling catheters. However, when investigating the urine of MEC users you should do it when the device is changed collecting urine coming directly out of the urethra, not taking urine from the bag. The same is true for patients with indwelling catheters.

28.4.8.2 Irritative Complications

Irritation is a non-allergic reaction, mostly recognized as pink or red discoloration of the skin. A possible explanation is chronic irritation caused by urine leakage due to a device which is not fitting adequately, leading to maceration, ulceration, and subsequently causing polypoid masses [12].

Another explanation is that with a condom chronic venous congestion occurs secondary to extrinsic compression [13]. Differential diagnosis may include condyloma acuminatum, giant condylomas (Buschke-Löwenstein tumours), verrucous

carcinoma, squamous cell carcinoma and urethral carcinoma.

28.4.8.3 Allergic Complications

Such complications caused by latex are well known. The reaction is more pronounced than irritation and produces erythema, even immediate hypersensitivity is possible. It is a response to a naturally occurring protein in rubber latex occurring 5–30 min after exposure [8].

28.4.8.4 Compressive Complications

The lack of pressure and/or pain sensation as in most patients with SCI creates an increased risk of compressive complications. Compression may cause penetrating or non-penetrating lesions. Strangulation of the penis may occur if the patient was not assessed properly (e.g. not considering reflex erections) and the size of the MEC was wrong. There are also reports in the literature of gangrenous changes of the penis because of compression due to the condom [14–17].

28.4.9 Are There Contraindications Against an MEC?

When incontinence is caused by high pressure chronic retention, the use of MEC devices is absolutely contraindicated in order to prevent (further) damage to the upper urinary tract. These patients are managed better by other means, e.g. indwelling catheterization or intermittent catheterization. In patients with low pressure chronic retention and bladder acontractility MECs may be used, although, if the bladder fails to be drained, the frequency of UTI and consequent complications are increased.

28.5 Alternatives to MEC

Alternatives to MEC depend on the underlying cause of the urinary incontinence. The alternatives are primarily intermittent catheterization, indwelling catheterization, absorbent products/pads, surgery (e.g. male sling) or a penile clamp as a temporary measure for a short time (hours).

28.5.1 Is a Clamp/Penile Compressive Device an Alternative to MEC?

Clamps have been available for many years but there are no studies published that have evaluated the safety, comfort or effectiveness. Clamps are an effective option, but only for a short period of time (hours), and provided that cognitive ability, manual dexterity and bladder and genital sensation allow a safe use [18]. The complications of penile clamps include oedema, urethral or penile erosion, urethral stricture disease and ischaemia. Their use must therefore be approached with great caution [19]. The penile clamp is absolutely contraindicated in case of detrusor overactivity or low bladder compliance because a clamp can increase the risk of developing high intravesical pressure and consequently vesico-uretero-renal reflux [20].

However, for certain patients/social events a clamp can be good alternative, provided it is only used for a short time that means some hours according to clinical experience.

28.6 Conclusions

The male external catheter (condom catheter) is a valuable option to manage urinary incontinence when therapeutic options are not possible or not indicated. Long-term indwelling catheterization should be avoided. A prerequisite for satisfaction and success with the MEC is to select on the individual basis the appropriate system in regards to type (one- or two-piece-system), material, size and drainage bag. The only real contraindication is incontinence due to a chronic high pressure urinary retention (in this case catheterization is the method of choice).

Alternatives to the MEC are pads and the penile clamp. The penile clamp is restricted to short-term use (hours) and is a method for special situations only (e.g. theater visit).

For further information see EAUN's evidence-based guidelines for best practice in urological healthcare, male external catheters in adults (2016) and references [21–23].

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Part X

Minimal Invasive Treatment

Intermittent Catheterization (IC)

29

J. Todd Purves and Jessica C. Lloyd

Abstract

Catheter drainage of the lower urinary tract in patients with neurogenic bladder seeks to maintain low bladder pressures that protect the kidneys, minimize urinary tract infections (UTIs), and achieve dryness to prevent decubitus ulcers and for social reasons. In mild cases of neurogenic voiding impairment, timed voiding and assistive maneuvers can achieve these goals and should always be attempted prior to instituting catheterization. External devices, in the form of condom catheters, may be preferable for men, when low pressure incontinence due to poor outlet resistance is the dominant issue.

Patients who are unable to effectively empty their bladders in acute settings, such as immediately after spinal cord injury or during exacerbations of multiple sclerosis, and in chronic settings, due to long term neurologic conditions, such as spina bifida and unresolved spinal trauma, are the typical candidates for long term catheterization strategies. Drainage of the bladder may be done transurethrally on a scheduled regimen or may be left indwelling for a specified length of time with periodic replacement. Alternatively, catheter drainage may be achieved percutaneously via a suprapubic approach.

29.1 Indwelling vs. Intermittent Catheterization

Indwelling catheters for long term bladder drainage have been commonly employed since the invention of the Foley catheter in the 1920s. Indeed, indwelling catheters are still commonly used today, likely because they can be managed by nursing staff with little to no intervention by urologic specialists. Catheter placement is taught in many nursing training programs and is typically considered a routine procedure within nursing scope of practice.

However, complications associated with indwelling catheters are myriad, including: UTIs, stone formation, inadequate drainage due to blockage, leakage around the catheter, increased risk of squamous cell carcinoma, long term renal dysfunction and erosion of the bladder neck and urethra [1]. Many of these problems can be avoided or minimized by switching to an intermittent catheterization program [2]. However, patients who have difficulty catheterizing due to aberrant anatomy, poor manual dexterity, inadequate cognitive capacity and lack of caregiver support may still be well served by maintaining an indwelling catheter. In this patient population, regular monitoring for adequate drainage and routine exchange to prevent biofilm and stone formation is critical. Studies that inform an optimum time interval for catheter exchange are lacking so, in practice, this can depend on clinical factors such as frequency of UTIs and social issues including proximity to medical providers and the cost of the devices.

Placement of a suprapubic indwelling catheter does require a moderately invasive procedure but is most clearly superior to transurethral catheters with regards to preventing urethral and bladder neck erosion as well as decreased risk of epididymitis, scrotal abscesses, and urethral fistulae [3]. They may be particularly suited for patients who cannot catheterize through the urethra due to strictures or other obstructions. Although there may be an increased risk of bowel or bladder injury when placing and using these devices, the incidence appears to be relatively low. With regards to other complications associated with urethral indwelling catheters, there is not significant evidence to claim a definitive advantage to the suprapubic approach. Urinary tract infections are the most common complication of indwelling catheters and they are extremely frequent regardless of the route of entry [4]. In theory, placing the tube away from the bacteria laden perineum should prevent or slow the formation of biofilms on the device but no

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_29

adequately powered randomized, controlled trial has proven this to be true [5]. Avoidance of upper tract deterioration, including vesicoureteral reflux and hydronephrosis, has been suggested in some retrospective trials but there is simply not enough confirmatory data to support this as an advantage for suprapubic tubes [3, 6]. In the subset of neurogenic bladder patients where indwelling catheterization is appropriate and who feel that this is more comfortable than urethral catheterization or whose anatomy or predilection for erosion is high, the suprapubic tube may be a reasonable management choice. However, this should not be promoted as a method that minimizes all of the complications commonly associated with long term indwelling urethral catheters.

In the early 1970s, Jack Lapides revolutionized the standard of care for management of neurogenic bladders when he introduced clean intermittent catheterization (CIC) as a practical means to maintain long term bladder drainage [7]. This technique has been documented as far back in history as ancient Egypt but had fallen out of favor early in the last century with the adoption of modern aseptic techniques. In the 1940s, neurosurgeon Ludwig Guttman of the Stoke Mandeville Rehabilitation Center in the UK, introduced the concept of intermittent catheterization for the management of urinary retention in spinal cord injury patients [8]. His sterile, no-touch technique demonstrated superiority over indwelling suprapubic catheterization with regards to urinary tract infection and urethral trauma. However, his method was not universally accepted by the urologic community for several decades after its first description. Lapides' innovation of clean, as opposed to sterile insertion, allowed greater acceptance of the IC treatment strategy.

Recently, two Cochrane reviews were performed to determine whether intermittent catheterization had proven benefit over indwelling urethral or suprapubic catheters for the long term management of (a) all patients and (b) of patients specifically with neurogenic bladder dysfunction [5, 9]. Both searches found zero randomized or quasi-randomized publications and the authors concluded that there was insufficient evidence upon which to base policy recommendations. Nonetheless, there is popular consensus that—IC is associated with fewer complications, including bacteriuria and UTI, pyelonephritis, epididymitis, vesicoureteral reflux, hydronephrosis, urethral trauma, urinary stones, squamous epithelial bladder cancer and autonomic dysreflexia compared to indwelling devices [10]. While much of this evidence comes from studies involving non-neurogenic patient models, the use of IC has become the standard of care for patients with myelomeningocele and spinal cord injury [11].

When patients are incapable of effectively emptying their bladders, the accumulation of urine generates high storage pressures that have deleterious effects on host defense mechanisms that protect against uropathogens [12]. Compression of the vasculature within the bladder wall creates a condition of hypoxia and this, along with direct pressure and stretching of the urothelium, can compromise the barrier function within the lumen. Further, these effects have been shown to initiate an inflammatory process via activation of the NLRP3 inflammasome [13]. Taken together, these factors culminate in an increased risk for urinary tract infection. Periodic emptying of the bladder limits sustained intravesical pressure and thereby reduces susceptibility to uropathogens. Indwelling catheterization can also achieve this goal, but at the expense of biofilm formation that increases the bacterial population in the lumen, while also mechanically damaging the urothelium and diminishing its protective capability [14]. Thus, the predominant theoretical advantage of IC over indwelling devices is avoidance of UTIs.

While properly powered randomized, controlled trials that show definitive benefit of IC over indwelling catheterization in UTI prevention have yet to be performed, several series strongly suggest such a benefit. A small study that randomized 40 patients each to either IC or indwelling urethral catheterization (IUC) demonstrated lower rates of pyelonephritis [15]. Their randomization procedure was poorly described and the study was underpowered to investigate most significant relevant end points, such as deterioration of renal function. However, they did show that IC was associated with a much lower rate of pyelonephritis, 5% over a 6 month period versus IUC with a rate of 25% over that period. The population was overwhelmingly (91%) male and the etiology of bladder function was neurogenic in two thirds. There appeared to be an advantage for IC in terms of epididymitis and urosepsis as well but this did not reach statistical significance. While the methodology of this study was questionable, it does represent a unique attempt at a randomized trial to determine the relative merits of IC versus IUC.

Two series, one retrospective and one prospective, provide a comparison of IC versus IUC for long term bladder management of spinal cord injury patients. The latter followed 128 patients (100 males, 28 females) with SCI for 38 months and focused specifically on developing UTI as the primary endpoint [16]. Over 3½ years, the overall incidence of UTI was 0.68 episodes per 100 patient-days in the IUC group compared to a significantly lower rate of 0.41 for the IC group. The odds ratio for UTI development was 1.53 for patients relying on an indwelling catheter. In Weld and Dmochowski's retrospective series on 316 SCI patients, the mean follow up time of 18.3 years provides a much longer-term picture but there was considerable crossover among the management groups [17]. Clinically, they observed several urological complications with IUC, including pyelonephritis, epididymitis, urinary stones of the upper and lower tracts, urethral strictures and abscesses, as well as radiological deterioration of the upper tract and vesicoureteral reflux. They found that 53.5% of patients dependent upon IUC experienced at least one complication of some type versus only

27.2% in the IC cohort. Lower urinary tract infections were not included in their list of complications and the authors note that 94% of the study population was treated for infectious cystitis regardless of bladder management strategy. However, the rate of pyelonephritis was significantly lower when IC was used compared to IUC. Despite the shortcomings of both of these studies, they do strongly suggest the superiority of IC over IUC in the long term management of bladder dysfunction in SCI patients.

Randomized, controlled trials of IUC versus IC have been performed over short time periods following brief intervals after orthopedic and urogynecologic surgery [18, 19]. These have demonstrated an advantage in preventing UTI and perhaps more importantly, a shorter duration of catheterization after invasive procedures. While there is little direct relevance to the chronic condition of neurogenic patients, this study may be applicable to patients with acute spinal cord injuries who are still within the time frame of spinal shock. IC allows for clinical evaluation of the patients' functional status at an earlier stage so that diagnostic work up can proceed and long term treatment strategies may be implemented as soon as possible.

SCI can produce poorly compliant bladders, outflow resistance due to detrusor-sphincter dyssynergia (DSD), vesicoureteral reflux and high backflow pressures on the kidneys. Until the advent of modern urologic management for neurogenic bladder, renal failure was a primary source of morbidity and mortality in these patients [20]. Despite the improvement seen with regular bladder drainage, it was soon evident that patients with properly functioning long-term indwelling catheters, either trans-urethral or suprapubic, often suffered from high rates of upper tract deterioration [21, 22]. While some later studies suggested these rates were not as high as previously suggested, these did not include controlled groups to indicate whether IC might provide an advantage [23, 24]. A study by McGuire and Savastano found that upper tract abnormalities demonstrated on intravenous pyelography occurred in over half of their patients with IUC but in none of those using IC for 2–12 years [25]. More recent studies, such as those done by Weld and Dmochowski in 2000 and by Zhang and Liao in 2014, found that the risk of developing upper tract abnormalities on imaging was reduced by over half when using IC instead of IUC or SPT [17, 26]. The detriment of IUC may be due to the chronic inflammation caused by the mechanical trauma of the permanent catheter, leading to diminished detrusor compliance coupled with subclinical detrusor overactivity [17]. Indeed, an investigation where ambulatory urodynamics was performed on patients with IUC for a mean of 14 years found that dangerous storage pressures were evident even in those with freely draining catheters [27].

While there are sufficient data to recommend IC over IUC, there are many social, financial and medical (such as the presence of autonomic hyper-reflexia) reasons that prevent some individuals from accepting an intermittent catheterization regimen. These patients may be managed with IUC or SPT and with sufficient monitoring; their incidence of renal failure is quite low even when evidence of kidney scarring or hydronephrosis is present [6, 28, 29]. As discussed elsewhere, SPT may be preferable with regards to certain complications such as urethral erosion, and at least one study found it to be superior to IUC in terms of protecting the upper tracts. However, in a recent meta-analysis SPT did not prove to be superior to IUC for upper tract preservation [3]. Therefore, either method can be considered a second line of therapy behind IC.

An association between indwelling urinary catheters and the development of bladder cancer, particularly squamous cell carcinoma has been known since the 1970s. A long term risk of 8–10% has been determined in several studies [30–33]. The increased risk of cancer is likely due to a state of chronic inflammation that stems from catheter trauma itself, stone formation or recurrent UTIs. Surveillance regimens for patients with indwelling catheters lack sufficient supporting data but most urologists advocate annual cystoscopy starting 8 years after placement [33]. To date, there has been no increased risk of bladder cancer found in patients performing IC and this is a clear advantage for advocating an intermittent regimen.

IC presumably has several advantages over IUC, including a lower complication rate, freedom from appliances and ability to pursue sexual activities, which should afford patients a higher quality of life. Indeed, a study by Adriaansen and colleagues demonstrated that SCI patients performing IC had improved quality of life scores on validated instruments relative to those dependent on IUC [34]. However, it is important to realize that other studies report that IC nonetheless does have an adverse impact on quality of life relative to spontaneous, volitional voiding. This can be a source of patient non-compliance with the treatment regimen [35]. While compliance is relatively good in the short or intermediate term, Chai, et al. found that their compliance rate fell to 71% after a mean follow up of 5.9 years [36]. Considering that patients may be required to catheterize for decades, this is an ominous finding and is supported by Husmann's finding that renal deterioration in adult spina bifida patients after bladder augmentation was most predicted by noncompliance with a IC regimen [37]. Therefore, it is imperative that medical providers optimize the conditions that enhance compliance. This begins with patient selection to ensure that the patient has suitable dexterity, vision, anatomy and cognition to make IC possible and not too burdensome. In young children or severely debilitated patients, catheterization is often performed by a family member or auxiliary provider who should have readily available support from the specialized urologic team. Access to providers who can teach technique

and troubleshoot difficulties as they arise along with easy procurement of equipment from suppliers can have significant positive impact on treatment participation.

Despite a lack of large scale randomized clinical trials to compare IC versus IUC, sufficient data does exist to support IC as the gold standard for neurogenic bladder patients who require urinary drainage. Both the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America promote IC in their guidelines to prevent catheter acquired urinary tract infections (CAUTI), though both are acknowledged as weak recommendations based on the quality of the evidence [38, 39]. Recommendations from the Neurologic Incontinence Committee of the Fifth International Consultation on Incontinence include the use of intermittent catheterization prior to instituting indwelling catheters and propose the usefulness of IC in achieving continence in patients who are capable of doing so [10]. In the United States, the Centers for Medicare and Medicaid Services incentivized the use of IC in its decision to discontinue reimbursement to hospitals and providers for the treatment of CAUTI on October 1, 2008 [40]. The CMS definition of CAUTI requires the presence of an indwelling catheter, so cost related to UTIs that occur in patients undergoing IC continue to be covered. As institutional protocols are now in a rapid state of revision, it is likely that this financial incentive will encourage greater usage of IC over indwelling catheters.

In Europe, guidelines for intermittent catheterization have been formalized by the European Association of Urology [41]. They offer a grade A recommendation that indwelling transurethral and suprapubic tubes should be avoided and that intermittent catheterization is the preferred intervention for patients who are unable to empty their bladders. They suggest that a 12–16 Fr catheter should be employed, on average, 4–6 times per day to produce a maximum of 400–500 mL of urine per each drainage. Further they address technical aspects of catheterization including sterile, aseptic and clean techniques. Sterile technique is predominantly used only in the setting of the operating room or intensive care units. Clean catheterization, popular in the USA and in pediatric populations was felt to lead to higher rates of UTI. Therefore, the EUA recommends the use of aseptic technique which includes the use of a sterile catheter and disinfection or cleansing of the genitalia. In addition, they advocate the non-touch technique which obviates the use of sterile gloves. The European Association of Urology Nurses has published a superb reference on the details of each of these techniques along with educational information for patients and their caregivers [42].

29.2 Technique: Sterile/Aseptic/Hygienic (Clean)

Three general techniques for intermittent catheterization exist, including (1) sterile, (2) aseptic, and (3) clean catheterization. Sterile technique employs all sterile materials, catheter, gown, gloves while using formal antiseptic dressing and drapes as one would encounter in the operating room. With aseptic technique, sterile catheters and lubricant are used along with cleansing of the genitalia. When using the "non-touch technique" that utilizes a specialized pull-in aid or package that that allows catheterization without any direct handling of the catheter; no sterile gloves are necessary. Females may have some difficulty with inserting the catheter without any handling of the tip and while they may sometimes master this technique, it is especially useful for male patients. Clean technique may use either a sterile catheter for the first use or a previously used catheter that has been washed in soap and water. For studies, clean non-sterile gloves are often donned but in practice, washing the hands prior to insertion is sufficient. There is no preparation of a sterile field or cleansing of the meatus with antiseptic but daily hygiene is typical. Clean catheterization is infrequently used in medical facilities where the risk of infection is greater than in the home setting.

Few randomized trials have been conducted comparing the use of sterile, aseptic and clean insertion techniques with a focus on infectious outcomes [43]. Variations of technique and catheter type across studies do occur and sometimes provide difficulties to compare their findings. Further confusion is added by mixed use of terminology, for example referring to aseptic technique as "sterile". Therefore, we will focus on those studies with clearly performed strategies that allow a direct head-to-head comparison.

Three randomized trials have queried the relative benefits of clean versus aseptic technique. Each used uncoated, non-prelubricated catheters in each study arm. King et al. found a very slight advantage for the sterile method in incidence of symptomatic UTI (0.43 vs. 0.59 daily probability) and time to onset of UTI (1.12 vs. 1.12 weeks) but the small study size did not produce results that were statistically significant [44]. Duffy and colleagues' study in a long term care setting also found no significant difference in incidence or time to onset of symptomatic UTI with respect to the type of insertion method used [45]. A study of spinal cord injured patients by Moore used sterile, single-use PVC catheters in both arms and found no significant difference in insertion type with respect to development of UTI or asymptomatic bacteriuria [46]. Both of the studies by Duffy and Moore also performed a cost analysis and recommended clean technique as a potential for health cost savings, considering equal outcomes.

A variation on aseptic catheterization is the non-touch technique which uses specialized equipment to allow performance of the procedure without donning sterile gloves [8]. Although many different products are available worldwide, they typically all consist of a pre-lubricated catheter contained within a collection bag. The catheter can then be pushed out of the bag and then inserted into the urethra, with or without the aid of an introducer, without the practitioner

handling the catheter itself. Randomized control trials comparing the safety of non-touch technique to conventional aseptic or clean methods are lacking. However, a prospective study of 18 SCI patients found that over a 7 month period, there was a 45% decrease in the incidence of UTI [47]. They also surveyed the nursing staff who reported that the non-touch technique was easier to set up, perform and clean up than the standard aseptic method. Despite a paucity of literature to support the non-touch technique it does stand to reason that eliminating catheter handling as a route for infection should lead to decreased UTI. For patients or caregivers with sufficient manual dexterity and particularly for male patients in whom the method is easier to perform, this is an excellent alternative for many patients.

29.3 Coated vs. Non-coated Catheters

Plain uncoated catheters are usually made of PVC or silicone and can be single or multi-use devices. When used more than once, they are typically washed with soap and water and air dried after each catheterization. Without additional lubricant, the high friction of uncoated catheters can cause discomfort and significant trauma to the urethra. For each attempt at catheterization, single packets of sterilely packaged water based lubricant can be employed as a single use product. However, when applying the lubricant to the catheter, most of it is pushed to the side of the meatus with insertion. To remedy this, products such as Instillagel® or Cathejell® are packaged with an insertable tip to allow for the lubricant to be injected into the urethra which has been shown more effective in overcoming friction and resistance. These pre-packaged lubricants consist of water soluble jelly with or without an antiseptic, such as chlorhexidine, and analgesics, of which lidocaine is the most common. Theoretically, such formulations should increase comfort and decrease bacterial inoculation but there are currently no sufficiently powered studies that support that assertion. In several studies comparing lidocaine infused gel with plain lubricant prior to performing office cystoscopy, there did not appear to be a significant advantage in terms of comfort and in fact may cause more discomfort [48–50]. For patients who have a sensate urethra, it may be wise to have each individual patient trial several of the available products to determine which is best for him or her.

In an attempt to decrease resistance to insertion and lessen urethral trauma without requiring additional lubricant, catheters coated with a hydrophilic outer layer have been developed. These cannot be cleaned or reused so they are restricted to single-use protocols. Several studies have sought to compare the use of plain versus coated catheters with regards to development of UTI, bacteriuria, urethral trauma and bleeding and patient satisfaction [43]. As encountered in other trials of catheterization parameters, the variability in type of product and technique of insertion hampers direct comparison between studies.

Two randomized clinical trials have investigated the use of single-use sterile catheters versus multiple-use clean catheters while employing a clean insertion technique for both study arms [51, 52]. Neither study found a statistically significant difference in rates of hematuria or patient satisfaction rates between either catheterization device or protocol. The study by Kiddoo did demonstrate a lower rate of UTI in the patients using a multi-use PVC catheter, but they note that their study was underpowered due to recruitment difficulties. A randomized trial where the same type of plain uncoated catheter was used by groups utilizing single use versus multi use protocols found no difference in rates of bacteriuria [53]. It is important to note that these studies were comparing not only different products, that is coated versus uncoated catheters, but also different protocols for usage, single versus multi-use.

In an effort to directly compare the performance of coated versus uncoated catheters, four centers have eliminated the protocol difference by comparing single use hydrophilic catheters to plain, uncoated catheters that were also used only once [54–57]. Two of the four found a significant difference in symptomatic UTI, with an approximate 20% reduction in favor of the coated catheters [56, 57], while the other two did not. In the three studies where bacteriuria was measured, no statistical difference between catheter types was found [54–56]. Two of the studies found that the hydrophilic catheters caused less hematuria and that the patient satisfaction rate for these devices was superior to the plain [54, 55]. In summary, results are mixed regarding UTI complications with half showing a significant reduction and the other half failing to do so. Importantly, in no study was the uncoated catheter found superior with regards to infection. In the studies where trauma and patient satisfaction were measured, the results were consistently in favor of the hydrophilic coated catheters.

A third commercially available device includes an uncoated but pre-lubricated catheter where a gel reservoir in the package serves to apply lubricant to the catheter surface. The two studies that have looked at them suggest that patient satisfaction is higher with these than other products [55, 58] and that urothelial trauma as measured by hematuria or urothelial sloughing was diminished. However, only one found that pre-lubrication decreased UTI and bacteriuria rates [58]. A third study compared an uncoated, pre-lubricated catheter (InCare®Advance Plus) with two hydrophilic coated catheters (SpeediCath® and LoFric®) and found that rates of hematuria were lower and patient satisfaction rates were higher with the coated catheters. Interestingly, the Speedicath® but not the LoFric® catheters demonstrated a lower withdrawal friction force in comparison to the InCare®. This suggests that performance rates may differ not only between catheter types, but also between different products within the same class.

Data from the clinical trials has been differently interpreted by experts and their governing bodies. For example, in Europe the perception of the evidence is that coated catheters reduce the risk of UTI, and thus the need for antibiotics, as well as prevent urethral trauma. Therefore, the encouraged practice favors the use of coated catheters. On the other hand, in the United States, the data is interpreted as weak and so the decision regarding which catheter type to use, particularly in pediatric practice, is based on patient choice. In many cases, cost is a driving factor and here it is clear that plain catheters used multiple times are the least expensive from an equipment and supply perspective. However, a study by Bermingham found that the reuse of non-coated catheters was only more cost effective if less than four catheters were used per week [59]. Cost savings may also depend on adjunct supplies and the requirement for medical personnel when patients are unable to perform self-catheterization. When the cost of gloves, lubricant, antiseptics and nursing are included, the uncoated catheters may not represent a significant cost savings [60]. When reimbursement is not the sole determinant, the decision on which catheters to use and how many times they use them should be informed by patient choice.

29.4 PVC vs. Silicone Catheters

For much of the twentieth century, urinary catheters were made of latex, a hydrocarbon polymer derived from the sap of the Para rubber tree (*Hevea brasiliensis*). Natural proteins found in latex can induce a type-1 allergic reaction that can be fatal in susceptible people [61]. In the 1980s, partly due to the HIV pandemic, latex products saw a significant increase in usage and the emergence of latex allergies in patients and healthcare workers with frequent exposure became a known health risk. In the 1990s, studies found the risk of latex allergies to be as high as 30% in health care workers and upwards of 47% in adult spinal cord injury patients [62, 63]. As a result of this, latex has been largely abandoned as a urinary catheter material, particularly in patients with neurogenic bladders where chronic and frequent exposure carries a high risk of developing allergies [64]. The majority of commercially available devices are now made of either polyvinyl chloride (PVC) or silicone, both of which have been shown in a dog model to produce less urethral inflammation compared to latex [65].

PVC, synthesized from monomers of vinyl chloride, is hard and stiff in in its pure form and must incorporate plasticizers to produce necessary pliability and softness. One of these, DEHP (di(2-ethylhexyl)phthalate), has been shown to cause liver toxicity and testicular atrophy in lab animals [66]. Based on this knowledge, the US FDA issued a Public Health Notification for PVC in 2002 where they urge limiting exposure to PVC in developing males [67]. It is unclear how much exposure to DEHP occurs in humans who are using PVC catheters to perform IC as these studies are lacking. Another issue regards the environmental hazards posed by the disposal of PVC products. Particularly in hospital settings where biohazardous materials undergo incineration, PVCs can release toxic gases such as polychlorinated biphenyls and hydrochloric acid [68]. Despite these potential hazards, PVCs are significantly less expensive than alternatives and remain in common usage throughout the world.

Silicones are a family of synthetic polymers formed by repeating silicon to oxygen bonds [69]. They lack allergenic proteins and plasticizers which may leach out during usage. They are quite durable and may be particularly useful for multi-use catheterization regimens. However, the materials required for producing silicone are significantly more expensive than for either PVC or latex and so the cost of silicone catheters can be several-fold higher. Where health care resources are limited, the possible health and environmental risks of PVC may not be deemed of sufficient gravity to justify the added expense.

There are no head to head studies of silicone versus PVC catheters to determine which carries a lower risk of UTI and trauma or which has better patient satisfaction. One study did find that several species of enterococcus were more adherent to silicone than PVC [70]. However, the materials were exposed to the pathogens during an overnight incubation and it is not clear how relevant this would be with respect to intermittent catheterization. Currently the decision over which material to use will weigh the cost of the silicone against the possible health and environmental concerns with PVC. Mitigating the cost of silicone, however, may be its ability to be re-used without significantly increasing the risk of UTI, trauma and other complications [71]. Kovindha and colleagues reported on a group of 28 SCI patients who used the same silicone catheter for an average of 3 years and found minor encrustations and loss of stiffness but no significant obstructions. Therefore, even in developing countries, the trend towards using silicone catheters for intermittent catheterization may be feasible.

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Intravesical Drug Therapy

30

J. Todd Purves

First line therapy for detrusor overactivity in patients with neurogenic bladder consists of oral agents, most commonly antimuscarinics. However, many patients suffer from severe side effects such as dry mouth, constipation and heat intolerance and therefore cannot tolerate the systemic administration of these agents. Intravesical administration, which is simply introducing the drug directly into the bladder through a catheter, attempts to maximize the local action of the medication while limiting the systemic absorption and thereby decreasing the emergence and/or severity of side effects.

Intravesical administration of drugs has several advantages and disadvantages when compared with oral administration. Directly instilling the agent into the bladder allows for direct exposure in the target organ and in concentrations that are higher than is possible when given orally. Decreasing the systemic concentration and bypassing the liver avoids the first pass effect which should eliminate or diminish side effects [1]. Unfortunately, there are several challenges to utilizing the intravesical route. The most important issue is the relative impermeability of the lining of the bladder, due to the glycosaminoglycan layer and the tight junctions between the umbrella cells of the urothelium. Penetration of molecules into this layer is dependent on their molecular weight (with smaller molecules having greater access), the pH, and their relative hydrophilicity/hydrophobicity; so not all compounds are candidates for this route. Further, any agent instilled into the bladder will be diluted by the urine and will be washed out of the bladder by the normal catharsis of urine. This issue can be helped by restricting fluids during administration to slow the rate of urine production. Finally, administering drugs via the bladder requires catheterization which is more invasive and less convenient than oral ingestion. Since most patients with neurogenic bladders perform routine intermittent catheterization, this is not an insurmountable barrier for this population.

The only commonly used intravesical drug therapy for neurogenic patients is the direct administration of oxybutynin which can be used as an adjunct to oral therapy or as a second line therapy in patients unable to tolerate oral antimuscarinics. Based on drug delivery studies in a pig model, it appears that the drug acts locally, at the muscarinic receptors in the urothelium and the nerves within the mucosa rather than within the detrusor [2]. Schroder and colleagues performed a randomized controlled trial of instilling 10 mL of 0.1% solution of oxybutynin three times daily versus oral oxybutynin three times daily in patients with neurogenic bladder for 28 days [3]. They found that bladder capacity was significantly increased in the intravesical group compared to the oral group, 118 mL vs. 18 mL and the side effects were drastically reduced. Most of the patients in the intravesical drug treatment group continued the regimen at the end of the study period, suggesting that the method was well tolerated.

In children with neurogenic bladders, oral antimuscarinic therapy can be especially difficult because the extended release compounds for oral administration can be formulated at doses that are not appropriate for smaller patients. Also, there is a growing concern about the long term negative effects of antimuscarinics on cognition [4]. Therefore, intravesical therapy is particularly attractive for the pediatric population. A recent study by Humblet followed children with spina bifida undergoing intravesical oxybutynin therapy for 15 years [5]. Their patients received a dose of oxybutynin 0.2 mg/kg body weight twice daily which was administered via the urinary catheter during intermittent catheterization. Over the course of the study, the observed bladder capacity in these children increased from the bottom 5th percentile to 25–50th percentiles in their age group and there were positive effects seen in bladder compliance. Mean end filling pressures dropped to safe levels which is an important factor in protecting renal function in this population. This study confirmed the usefulness and safety of intravesical oxybutynin for treating neurogenic bladder dysfunction in children.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_30

Botulinum toxin has emerged as a powerful therapy for neurogenic bladder but its potent systemic toxicity requires a direct approach for administration. Currently, Botox must be injected intravesically due to the fact that the large botulinum toxin molecule is too large to cross the impermeable lining of the bladder. This procedure must be performed by a trained cystoscopist in the clinic or in the operating room and carries the risks of post-operative bleeding and/or improperly placed injections that do not deliver the drug in the correct location. Intravesical instillation would improve this approach but is hampered by the inability of the toxin to cross the urothelial lining. Several strategies are under development to overcome this problem but none are used in clinical practice at this time.

Nanoparticles, structures with features on the nanometer scale, offer a means for delivery of botulinum toxin that can enhance the concentration of the agent at the bladder lumen interface and also facilitate its movement across the urtothelial barrier. A promising class of these particles is liposomes, consisting of a bilayer of phospholipids arranged with a hydrophilic core, which can be impregnated with toxin. Liposomes have an affinity for the GAG layer of the urothelium and will congregate at the surface. Transport across the barrier is aided by endocytosis of the particles into the urothelial cells, carrying the impregnated therapeutic along with it. Studies with empty liposomes suggest that even the empty, non-impregnated, vehicle is capable of suppressing bladder overactivity in a rat model of chemical cystitis [6]. This action is likely due to the formation of protective lipid layer at the surface that protects the urothelium and underlying nerves from irritants in the urine. There may also be an anti-inflammatory effect related to local lipid signaling and subsequent mast cell action [7]. However, the most promising application of liposomes appears to be as a vehicle for the delivery of botulinum toxin.

Chuang and colleagues demonstrated that botulinum toxin impregnated liposomes, when instilled into the bladders of rats, results in cleavage of SNAP-25 and inhibition of the expression of calcitonin-gene related peptide in afferent neurons [7]. This also protected the animals from bladder overactivity when a chemical cystitis was induced. Based on that pre-clinical data, two clinical trials have been done with patients. A double blinded, randomized pilot study of 24 patients with overactive bladder compared the instillation of sphingomyelin based liposomes impregnated with botulinum toxin A to instillation with normal saline [8]. Patients exposed to the lipotoxin experienced decreased urinary frequency and urgency 1 month following treatment but there did not appear to be a decrease in SNAP 25 expression in the urothelium. While this study suggests clinical efficacy of botulinum, the lack of cleavage of SNAP 25 poses some uncertainty regarding the mechanism by which this works. A second, two institution study involving the same group, using the same treatment and control groups with 31 patients in each, found similar clinical efficacy for reducing urinary frequency and urgency [9]. As with the pilot study, there did not appear to be a significant risk of elevated post void residual or urinary tract infection. While early investigations support the potential clinical use of liposome-delivered botulinum toxin for patients with overactive bladder, further development will require larger patient trials and a better mechanistic understanding of the process. Also, neither of the clinical trials included patients with neurogenic bladders and so a dedicated trial that includes those patients must be introduced before this therapy will join the neuro-urologist's armamentarium.

Physical methods based on iontophoresis or electrophoresis techniques have also been investigated as a means to overcome the transport barrier presented by the urothelial barrier. Electromotive drug administration (EMDA) utilizes an electric field that drives an electrochemical gradient to enhance diffusion of the therapeutic agent. The electrical field is generated between an electrode attached to the catheter within the bladder and another attached to the skin of the abdominal wall. In a rabbit model, Kajbafzadeh et al. compared the distribution of botulinum toxin in the bladder mucosa, lamina propria and muscle after Botox injection versus EMDA [10]. Using a total dose of 10 IU/kg in each arm, they found that EMDA resulted in homogenous distribution of the toxin throughout the tissues versus a heterogeneous pattern encountered in the injection group. Based on their preclinical data, the same group of researchers performed a single armed clinical study, administering 10 IU/kg of botulinum via EMDA to 15 children with spina bifida [11]. Videourodynamics studies at 1, 4 and 9 months after instillation demonstrated a significant increase in bladder capacity with a decrease in maximal and end-point pressures with a concurrent decrease in urinary incontinence in 80% of the patients. Interestingly, 7 of the 12 children with vesicoureteral reflux had a decrease in the grade of reflux and 10 of the 12 children with fecal incontinence experienced an improvement from a bowel function standpoint. If future randomized controlled trials confirm these results, EMDA could be of particular benefit for the pediatric neurogenic bladder population by eliminating the need for general anesthetic when performing these procedures.

With the exception of direct instillation of oxybutynin, intravesical drug therapy for detrusor overactivity in the neurogenic population remains at the investigational stage and has yet to achieve widespread clinical acceptance. Future areas of study include the optimization of the delivery method and the choice of therapeutic agent. With regards to the former, several polymers are under development for use as indwelling devices that can act as a depot for therapeutic agents [12]. Currently, problems with this approach include difficulty with expulsion of the material from the bladder via

micturition, serving as a nidus for encrustation or infection, and mechanical irritation of the bladder. Advancement of this strategy would provide a means to enable a sustained release of medication without the need for repeated instillation. With respect to the therapeutic agents, re-purposing of drugs already available in oral formulations, as well as novel compounds, offer the possibility of expanding our ability to treat neurogenic bladder dysfunction. Some promising agents such as the vanilloids, capsaicin and resiniferatoxin, demonstrated early promise but have failed to exhibit clinical efficacy that is equivalent to botulinum toxin injections [13]. However, there are a multitude of molecules that can be delivered through the intravesical route that have yet to be tested. Immunomodulating chemotherapeutics, such as tacrolimus, and gene silencing nucleotides in the form of siRNA or antisense oligonucleotides can be impregnated into liposomes or artificial polymer devices [12]. Initial work with these agents suggest a clinical application for the treatment of interstitial cystitis and pelvic pain syndromes but their potential for treating neurogenic detrusor overactivity remains to be explored.

While intravesical drug therapy currently plays a minor role in the management of patients with neurogenic bladder dysfunction, particularly in the cases where patients are unable to tolerate systemic antimuscarinics, the potential for this modality is vast. Improvements in the drug delivery methods, coupled with the emergence of new therapeutic compounds offers substantial promise in these patients where routine intermittent catheterization is already a standard component of their management.

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Intravesical Electrostimulation (IVES)

31

Helmut Madersbacher

31.1 History

Already in 1887 the Danish surgeon Saxtorph [1] described intravesical electrical stimulation (IVES) for the "atonic bladder" by inserting a transurethral catheter with a metal stylet in it and with a neutral electrode on the lower abdomen. In 1899 the Viennese Frankl-Hochwart and Zuckerkandl [2] stated that intravesical electrotherapy was more effective on inducing detrusor contractions than external faradization. In 1975 Katona [3] introduced and popularized this method for the treatment of neurogenic bladder dysfunction. Ebner et al. [4] demonstrated in cat experiments that intravesical electrostimulation activated the mechanoreceptors within the bladder wall. Further basic research was undertaken by Jiang et al. [5] who demonstrated in the animal experiment that IVES induced modulation of the micturition reflex due to an enhanced excitatory synaptic transmission the central micturition reflex pathway. The observed modulation may account for the clinical benefit of IVES.

The afferent stimuli induced by IVES travel along afferent pathways from the lower urinary tract to the corresponding cerebral structures. This "vegetative afferentation" results in the sensation of bladder filling/urge to void, with subsequent enhancement of active contractions and possibly also voluntary control over the detrusor (Fig. 31.1). Thus experimental studies have confirmed the mechanism of action and the optimal stimulation parameters at least in the animal experiment. IVES involves an artificial activation of the normal micturition reflex.

Colombo et al. [6] demonstrated that IVES also induces electrical changes on higher micturition canters, measured by electroencephalography (EEG). The evaluation of viscerosensory cortical evoked potentials after transurethral electrical stimulation has been proved to be useful in determining whether a patient is suitable for IVES or not [7].

31.2 Technique

The technique involves a wire electrode (cathode) which is inserted into a transurethral or suprapubic catheter and connected to a stimulator. Saline (0.9%) is used as the current leading medium within the bladder. The anode (neutral) electrode is attached to the skin in an area with preserved sensation, usually in the lower abdomen. Mostly intermittent stimulation with bursts and gaps that can be varied (1–10 s) along with the rise time and the time of the plateau within the burst is applied. With intermittent electrostimulation, each therapy session takes 60–90 min, with continuous stimulation 20 min once daily, 5 days a week, until the maximum response is reached.

For patients who have never experienced the urge to void—e.g. children with myelomeningocele or children who have list tis ability—IVES is combined with biofeedback training: on a water manometer attached to the system the patient is able to observe the change in the detrusor pressure. This way he is able to realize that the sensation experienced I caused by a bladder contraction. This external feedback also facilitated achievement of voluntary control (see Fig. 31.2).

31.3 Results

The results presented are based on 33 studies: six are basic research papers (animal experiment and clinical research), one is a randomized controlled trial, there are two reviews within an editorial, one pro and one contra IVES, and the others are case series.

Intravesical electrical stimulation of the bladder is still a controversial therapy for patient with neurogenic detrusor dysfunction, although basic research has evidenced the

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_31

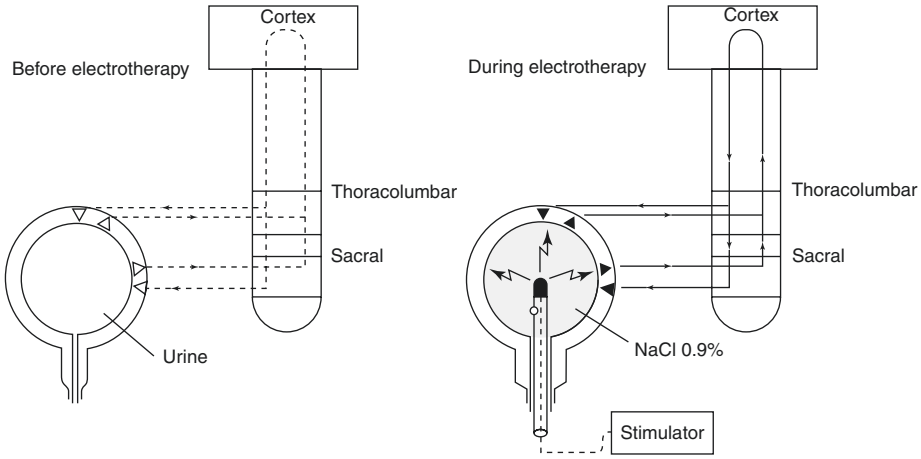

Fig. 31.1 Intravesical electrostimulation activates the mechanoreceptors within the bladder wall, thus increasing the efferent input from the bladder and consequently the efferent output to the bladder [4]

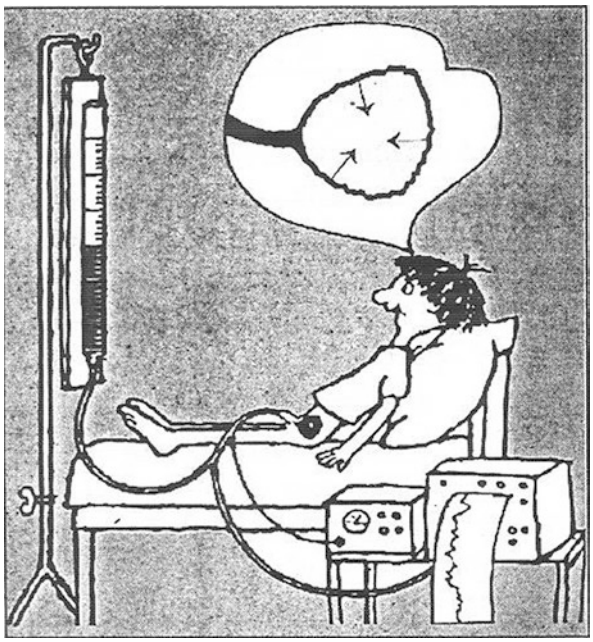

Fig. 31.2 With intravesical electrostimulation a feedback training is mediated by enabling the patient to observe the change of the detrusor pressure on a water manometer: the patient is able to realize when a detrusor contraction takes place

mechanism of its action and its efficacy. This controversy is also reflected in an editorial published in which Kaplan et al. [8] reported favourable results in 288 children who received at least one series (20 outpatient sessions, 90 min long): 87% of patients have control and void or catheterize with sensations or have improved bladder compliance. Eighteen percent have gained full control, they void synergistically and are continent. Finally, in 13% the treatment failed, but the patients maintained their condition.

According to Katona [9] from 1958 to 1991 in adults and MMC children better results were published with the average of 80 sessions in 802 patients.

In contrast, the results reported by Decter et al. [10] were less favourable in 25 patients during a 5-year period with altogether 938 sessions of stimulation. In a response to a questionnaire, 56% of parents noted a subjective improvement in their children's bladder functions. However, the urodynamic improvements achieved after IVES did not significantly alter the daily voiding routine in these children.

The only randomized controlled prospective clinical trial [11] could not find difference between active and sham treatment. However, only 15 sessions were performed at first and another 15 sessions of IVES were applied after a 3-month hiatus. Moreover, the inclusion criteria were not defined.

Other studies [12–28] are either individual case-controlled studies (LoE 3B) or case series (LoE 4). They cannot be compared to different or non-defined inclusion criteria, different technique details (different time span of electrostimulation, varying follow-ups), and some with only a small number of patients included.

Gladh [29] presented the results of 44 children (mean age 10.5 years), 20 of them with neurogenic bladder dysfunction: with a mean follow-up of 2.5 years, 64% had their bladder emptying normalized, 11 of 15 children on clean intermittent catheterization (CICI) have terminated catheterization, 8 of them with neurogenic bladder dysfunction; 7 children had nor remaining benefit of the treatment.

Recently Lombardi et al. [30] investigated the clinical efficacy of intravesical electrostimulation (IVES) in incomplete spinal cord patients suffering from chronic neurogenic non-obstructive retention (N-NOR). In this 15 year single-centre, retrospective study 102 patients were investigated who underwent at least 28 consecutive daily IVES. Thirty-eight patients (37.2%) responded to IVES and those (83.3%) recovered the first sensation of bladder filling after the IVES therapy. Nineteen responders repeated IVES within 1 year due to loss of efficacy. They obtained similar voiding symptoms, improvements and urodynamic results as after the first IVES cycle. The authors conclude that IVES represents a possible therapeutic option for incomplete SCI patients with N-NOR.

In another study, also Lombardi et al. [31] compared IVES with sacral neuromodulation in incomplete spinal cord

patients suffering from N-NOR. In this retrospective study 77 patients underwent IVES (minimum 28 sessions), then after returning to voiding baseline symptoms percutaneous First Stage of SNM was performed, lasting for minimal 4 weeks: 48 patients responded to neither of the treatments, whereas 29 responded to both, IVES and First Stage SNM. There was no significant statistical difference ($p > 0.05$) detected in the voiding diaries. There was a strict correlation in terms of clinical and urodynamic patterns in patients with incomplete SCI and N-NOR, following IVES and First Stage of SNM. However, voiding improvements through IVES was short-term when compared with the effects of permanent SNM.

31.4 Prerequisites for Successful IVES

None of the research really focuses on the inclusion criteria. According to the basic research, only those with at least some intact afferent fibers from the bladder to the cortex and with incomplete spinal cord lesions those with a presence of pain sensation the sacral dermatomes S3 and S4 can benefit from IVES.

31.5 Implications for Practice

Proper indication is crucial and this type of therapy should only be applied in those with some tact afferent fibers between the bladder and the cortex. If these premises are respected, IVES is effective.

IVES is safe. No side-effects have been reported, beyond and occasional urinary infection. The question of cost-effectiveness was raised by Kaplan, who stated that the most commonly used alternative for these patients is bladder augmentation, which is "miles apart in terms of cost, discomfort and short- and long-term complications" [8].

One benefit of IVES was noted by most of the authors: improved sensation documents satisfactory long-term results. The patients get already great satisfaction from knowing when their bladder is full and when it is time to catheterize or to void. Moreover, even without direct bowel stimulation, patients noted significant improvement in the warning of bowel fullness and improved control for their bowel movements.

31.6 Conclusions

Intravesical electrotherapy s able to improve neurogenic bladder dysfunction, primarily by stimulating Aδ mechanoreceptor afferents inducing bladder sensation and the urge to void and consequently by increasing the efferent output with improvement of micturition and conscious control.

IVES is the only available option to induce/improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage.

The potentials of IVES for bladder (re-)habilitation are still underestimated. Therapy is successful if the following prerequisites are fulfilled: incomplete nerve lesion, intact mechanoreceptors, a detrusor still able to contract a cortex able for perception of afferent stimuli, and experienced staff, place, time and patience. If these premises are respected, IVES is effective.

The ideal indication for IVES is the neuropathic underactive hyposensitive and hypocontractile detrusor.

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Percutaneous/Transcutaneous Tibial Nerve Stimulation

32

Grigory Krivoborodov

32.1 Introduction

Nowadays there are two types of electrical treatment of functional disorders of micturition—electrical neurostimulation and electrical neuromodulation.

In neurostimulation nerves are directly stimulated by electrical stimuli to achieve immediate responses. In neuromodulation electrical stimuli are applied to alter present neurotransmission processes [1]. In urology neuromodulation was initially pioneered using peripheral anogenital electrical stimulation. Advancement in technique has made neuromodulation a viable intervention first of all for patients with refractory detrusor overactivity. Several different methods of neuromodulation have yielded substantive benefit for those patients [2]. All types of neuromodulation are based on principles of long-time stimulation of required nerve pathways with using optimal electric current parameters from point of view of patient's sensation and comfort. Tibial nerve stimulation (TNS) is a minimally invasive method of neuromodulation for treatment of functional micturition disorders via delivering electrical stimulation to sacral nerve plexus through stimulation of tibial nerve [3].

Since mechanism of action of TNS provides restoration of lost of nerve control under the storage bladder function, this method is being considered as one of the most physiological and perspective way of treatment of overactive bladder (OAB).

32.2 History

TNS in treatment of patients with motor and sensory detrusor instability was reported by McGuire E.J. et al. in 1983. In the course of experimental studies on the inhibition of detrusor activity in nonhuman primates with spinal cord injury they noted that bipolar anal sphincter stimulation was effective only if current was delivered by needle electrodes to the sphincter muscle. They suggested the possibility to inhibit reflex detrusor activity with minimal current loss by applying a positive electrode to the anal sphincter with a negative electrode placed over tibial nerve. They found also that current could be applied via a positive electrode transcutaneously to the common peroneal or tibial nerve with a ground electrode placed over the contralateral common peroneal or tibial nerve with similar results.

Based on these experimental works they used that new application of electrical stimulation to inhibit detrusor activity in 15 patients with a variety of neural lesions. Therefore, stimulation was used to treat uncomfortable bladder urgency without detrusor instability and was successful in the majority of patients [4].

The method was further improved by Stoller M.L., who used the knowledge of classical Chinese acupuncture. The idea of stimulating of tibial nerve was based on traditional Chinese practice using acupuncture points over this nerve to inhibit bladder activity. In 1987 during experimental animal studies in pig-tailed monkeys Stoller M.L. demonstrated inhibition of spontaneous contractions of detrusor muscles after direct electrical stimulation of the tibial nerve [5].

Using a device of his own design to administer percutaneous tibial nerve stimulation (PTNS), he conducted a clinical study of patients diagnosed with urge incontinence, urgency/frequency syndrome and/or pelvic pain. Results were impressive with 89% of subjects responding to PTNS therapy. No serious adverse events or side effects were observed during or after treatments [6].

In 1999 he presented the first clinical data at the European Urological Association.

PTNS (Urgent PC, CystoMedix, Anoka, Minnesota) was approved by the Food and Drug Administration in 2000.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_32

32.3 Terminology and Classification

According to the wide range of literary recourses, there is a misunderstanding in definition of abbreviation "PTNS" which is used for defining tibial neuromodulation. Some authors often call PTNS as "posterior tibial nerve stimulation", but it's not correct because "posterior tibial nerve" doesn't exist at all. For better understanding and using correct definitions in terms of clinical practice and everyday life we give the anatomical chapter about tibial nerve and its brunches below.

Tibial nerve is a part of sacral plexus and origins from sciatic nerve, that's formed of L_{IV}-S_{III} nerve fibres. It comes from the popliteal fossa and following between the heads of the gastrocnemius muscle lies on the posterior surface of the popliteal muscle, and accompanied by the posterior tibial vessels passes under the tendinous arch of the soleus muscle, being here covered by the muscle. Heading further down under the deep leaf of the fascia of the lower leg between the lateral edge of flexor digitorum longus and medial edge of the long flexor of the big toe, tibial nerve reaches the posterior surface of the medial malleolus. After passing under the flexor retinaculum, the nerve divides into its two terminal branches: the medial and lateral plantar nerves [7, 8].

Actually PTNS means percutaneous tibial nerve stimulation. This implies that the tibial nerve is stimulated by electric current using a special thin needle inserted through the skin. The tip of the needle should be in the vicinity of tibial nerve.

The second option tibial neuromodulation is stimulation electric current tibial nerve with surface electrode located on the skin in its projections. Hence electrode-disc delivers electric force to the tibial nerve through the skin and soft tissues. This method is called transcutaneous tibial nerve stimulation. Thus tibial neuromodulation is performed in two ways: noninvasive (transcutaneous TNS-TTNS) or minimally invasive (percutaneous TNS-PTNS).

32.4 Mechanism of Action

The exactly mechanism of action of tibial neuromodulation is only partially understood. There is a point of view that the mechanism of action of electrical stimulation tibial nerve is complex and occurs at several levels. Matsuta et al. think that TNS might activate a reflex output to the bladder through the sympathetic hypogastric nerves and relax the detrusor via β-adrenergic mechanisms [9].

Well known that tibial nerve projects to the sacral micturition center and the nucleus of Onuf in the same area where bladder projections are found. For this reason TNS evokes a central inhibition of micturition pathways and the therapeutic effect takes place via these areas [10, 11].

32.5 Equipment

The system for TNS consists of three components, connected with each other with wires: active and passive electrodes and electric generator. Active electrode is a working part of the whole structure, which could be percutaneous and transcutaneous. Percutaneous electrode is a 34-gauge stainless steel needle, which connects with a electric generator. Transcutaneous electrode is a one side sticky disc with ability to pass the electric currency. Both percutaneous and transcutaneous electrodes are anodes, i.e. have positive charge.

Passive electrode is also one side sticky soft plate, often looks like transcutaneous active electrode. Its negative charge contributes in establishment of electric field, in which the active electrode is able to deliver its cure effect.

Electric current generator usually contains a battery of 9 V and a panel with regulators of current intensity, the frequency and duration of electrical pulses. All types of generators are able to change their setting: the amperage, frequency and time regime of electric impact.

32.6 Procedure

32.6.1 Percutaneous Approach

The standard place of stimulation has come from Chinese acupuncture, where usually the area of the Sanyinjiao (SP6) point is being used to treat pelvic floor organ dysfunction. Patients lie in supine position with the soles of the feet together and their knees abducted and flexed ('frog-position'). A 34-gauge stainless steel needle is inserted percutaneously for approximately 3–4 cm cephalad to the medial malleolus of the right or left ankle at the angle of 60° (between the posterior margin of the tibia and the soleus muscle tendon). A surface (passive) electrode is placed on the same leg near the

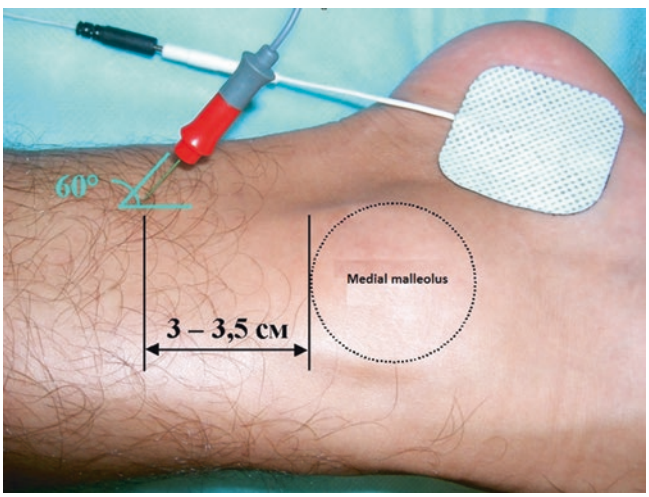

Fig. 32.1 Percutaneous tibial nerve stimulation

arch of the foot (Fig. 32.1). Fixed parameters are a pulse width of 200 μs and a frequency of 20 Hz. The stimulator contains a battery of 9 V. The amplitude is slowly increased until plantar flexion of the big toe or fanning of the all toes occur. If this response cannot be obtained or pain occur near the insertion site the stimulation device is switched off and the procedure is repeated. In most patients the motor response was accompanied by a sensory response as a radiating sensation spreading in the sole of the foot. The current was set at a well-tolerable level. Elevation of the current was allowed whenever fading of this sensation was experienced due to adaptation. Patients underwent 12 weekly outpatient treatment sessions, each lasting for 30 min. In case of a good response patients were offered chronic treatment [6, 12].

In general for caring out a complete course of treatment, patients undergo 30-min outpatient treatment sessions weekly for a period of 12 weeks. In case of sufficient improvement of their lower urinary tract symptoms (≥50% reduction of the number incontinence episodes and/or voids on bladder diary) patients are offered chronic treatment.

32.6.2 Transcutaneous Approach

With the patient sitting or lying on the back two adhesive surface electrodes placed in the region of the left or right of the medial malleolus of the ankle joint. A negative electrode placed on the medial malleolus and the positive electrode placed 10 cm above negative electrode, also on the medial side (Fig. 32.2). The rhythmic flexion of the toe during the stimulation determined the correct position of electrodes. The intensity level set below the threshold that causes motor contraction because the patient should be comfortable and no pain should occur during the procedure. Usually electrical stimulation of the tibial nerve performs for 30 min twice weekly over 12 sessions with a pulse rate of 10 Hz and a pulse width of 200 μs in continuous mode.

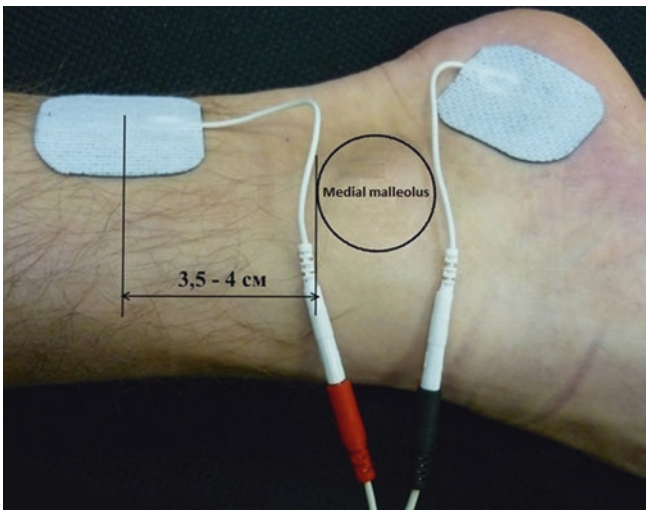

Fig. 32.2 Transcutaneous tibial nerve stimulation

In case of sufficient improvement of their lower urinary tract symptoms (≥50% reduction of the number incontinence episodes and/or voids on bladder diary) patients are offered chronic treatment.

This procedure can be carried out at home by a patient or one of his/her relatives. It is one of the major advantages of transcutaneous approach in compare with percutaneous one.

32.7 Indications

Nowadays official indications for TNS are very strict and don't capture all the positive aspects of this method. According to the Guidelines of European Association of Urologists 2016 PTNS are being prescribed just for female patients with idiopathic urge urinary incontinence, who has no benefits from anticholinergics. The effectiveness of tolterodine and tibial nerve stimulation is comparable in this category of patients [13].

Nevertheless there are some protocols and reviews, which demonstrate pretty good results regarding to both non-neurogenic and neurogenic lower urinary tract symptoms. They can include not only urgency and frequency, but also bladder empting disorders and chronic pelvic pain.

32.8 Clinical Data

32.8.1 TNS and Idiopathic OAB

There are some randomized clinical researches, with sufficient statistical significant data, which let us to consider this method as effective and safety.

One of them is by Finazzi-Agro E. et al. its data was published in 2010. PTNS was prescribed to 18 female patients with urge urinary incontinence due to idiopathic detrusor overactivity. Others 17 women received sham treatment. Previously all 35 patients didn't respond to antimuscarinic therapy. The sessions lasted for 30 min and were performed 3 times weekly, totally there were 12 sessions. All patients were evaluated with bladder diaries as well as quality of life scores before and after treatment. Finally in 15 (71%) patients in the group of treatment there was a significant improvement more than 50% in all parameters: the number of incontinence episodes, number of voids, voided volume and incontinence quality of life score. In placebo group there was not any positive changes [14].

The data of Peters K.M. et al. demonstrates positive results of PTNS in 220 adults with OAB symptoms. Patients were randomized 1:1 to 12 weeks of treatment with weekly PTNS or sham therapy. The 13-week subject global response

assessment for overall bladder symptoms demonstrated that PTNS subjects achieved statistically significant improvement in bladder symptoms with 54.5% reporting moderately or markedly improved responses compared to 20.9% of sham subjects from baseline ($p < 0.001$). All individual global response assessment subset symptom components demonstrated statistically significant improvement from baseline to 13 weeks for PTNS compared to sham. Voiding diary parameters after 12 weeks of therapy showed PTNS subjects had statistically significant improvements in frequency, nighttime voids, voids with moderate to severe urgency and urinary urge incontinence episodes compared to sham. No serious device related adverse events or malfunctions were reported [15].

In the research of Peters K.M. et al. published in 2013, the 3-year results of PTNS were evaluated. Fifty patients who met the primary effectiveness end point after 12 weekly PTNS were enrolled in prospective study to assess long-term outcomes. There were a special timetable for the patients with symptoms of overactive bladder, all of them had the anamnesis of effective and safe using of this method. All patients were prescribed a fixed schedule 14 week tapering protocol followed by a personal treatment plan aimed at sustaining OAB symptom improvement. A total of 29 patients completed the 36 month protocol and received a median of 1:1 treatments per month after a 14 week treatment tapering protocol. https://www.jurology.com/article/S0022-5347(12)05807-7/fulltext. Of course, participants were not prescribed OAB medications throughout the study. After 36 weeks the treatment was completed and the results of 29 patients were evaluated. It turned out that 77% of patients maintained moderate or marked improvement in OAB symptoms at 3 years. All the parameters: voids per day, nighttime voids per night, urge incontinence episodes decreased with statistical significance. All quality of life parameters remained markedly improved from baseline through 3 years (all $p < 0.0001$). There were not any serious adverse events in all patients [16].

There is an interesting publication showing that PTNS can be more effective or to have comparable results with antimuscarinics in the treatment of patients with OAB. In this study, the authors compared effectiveness of PTNS with antimuscarinic drugs. For that purpose 100 patients with OAB were randomized 1:1, so that half of them underwent weekly PTNS and the others received 4 mg of extended-release tolterodine. The whole treatment carried out during the period of 12 weeks. The global response assessment demonstrated that subject assessment of overactive bladder symptoms compared to baseline was statistically significant in the PTNS arm with 79.5% reporting cure or improvement compared to 54.8% of subjects on tolterodine ($p = 0.01$). Assessments by investigators were similar but did not reach statistical significance ($p = 0.05$). After 12 weeks of therapy objective measures improved similarly in both groups for reductions in urinary frequency, urge urinary incontinence episodes, urge severity and nighttime voids, as well as for improvement in voided volume. There were no serious adverse events or device malfunctions. Thanks to the results obtained in this paper, it is possible to go ahead in extension of this method among the physicians, especially if some of them try to avoid this procedure due to lack of evidence base. But this trial really let us think that PTNS is no inferiority in compare with anticholinergics in patients with overactive bladder. Other randomized researches are necessary for taking as much as possible data about this treatment option [17].

One of the works shows the possibility of using TTNS in elderly patients with OAB. There are some difficulties in elderly patients who take anticholinergic drugs, because of risk of side effects [18–20]. This group of patients is a special one, because it's necessary always keep in mind the concomitant therapy and associated diseases. That's why receiving of some antimuscarinic therapy and intradetrusor injections of botulinum toxin type A could be limited. In these cases TNS could be an alternative method for elderly people.

Schreiner L. et al. demonstrated advantages of combination TTNS together with bladder retraining and pelvic floor muscle exercises. Significant improvement of number of daily micturitions, nocturia, and number of urge urinary incontinence episodes was observed in TTNS group in compare with control one. Hence this method could be an effective and safe treatment even in elderly female patients, who often have some special demands [21].

Noteworthy work regarding the application of TTNS after positive results of PTNS. Maurelli V. et al. performed a flexible home protocol of TTNS at 16 patients with OAB who had responded to PTNS. Fourteen from 16 patients were followed up for a mean of 19.7 months. All patients were considered subjective responders and 13 had the improvement of objective parameters. The authors believe that home-based TTNS is a feasible option for patients who had good response to PTNS [22].

32.8.2 TNS and Neurogenic Detrusor Overactivity

Despite the tibial nerve stimulation is officially being prescribed only for patients with non-neurogenic urinary tract dysfunction, there are some researches, which show us its benefits for neurogenic patients. In the review of Schneider M.P. et al. there were screened 1943 articles, 16 studies (4 randomized controlled trials, 9 prospective cohort studies, 2 retrospective case series, and 1 case report) enrolling 469 patients (283 women and 186 men). These scientific papers included patients with multiple sclerosis, Parkinson's disease, cerebrovascular accident, incomplete and complete spinal cord injury.

After the detailed analysis, authors found out that the improvement of all parameters—maximum cystometric capacity, mean increase of bladder volume, mean decrease of maximum detrusor pressure during the storage phase, the mean decrease in number of voids per 24 h, in number of leakages per 24 h, and in postvoid residual—was achieved. No TNS-related adverse events have been reported [23].

Although preliminary data of randomized and non-randomized clinical trials suggest TNS might be effective and safe for treating neurogenic lower urinary tract symptoms, the evidence base is poor, derived from small, mostly noncomparative studies with a high risk of bias and confounding. More reliable data from well-designed randomized clinical researches are needed to reach definitive conclusions.

So, PTNS is a simple, effective and safe method for treatment patients with idiopathic OAB. Further research is needed testing PTNS and TTNS against a sham in order to discern the true efficacy of this treatment for neurogenic detrusor overactivity.

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Botulinum Toxin Injections in the Bladder and Urethral Sphincter

33

João Silva and Francisco Cruz

33.1 Introduction

Intravesical pharmacological therapy for lower urinary tract dysfunction may offer two potential advantages, a high concentration of pharmacological agents directly to the bladder tissue and the possibility of using drugs inappropriate for systemic administration due to off target effects. This is the case of botulinum toxin A (BTX-A). Intravesical pharmacological therapy with this toxin, while highly effective, should still be considered as a second line treatment in patients refractory to oral therapy or that do not tolerate its systemic side effects.

Botulinum toxin (BTX) is a neurotoxin produced by the bacterium *Clostridium botulinum*. There are seven subtypes of BTX (A to G) [1]. Sub-type A has the longest duration of action, making it as the most relevant for clinical use. In addition to sub-type A, some studies have investigated the effect of detrusor injection sub-type B, rimabotulinumtoxinB (proprietary names being Miobloc™ or Neurobloc™ according to countries).

BTX-A is available in different commercial forms, with the proprietary names of Botox®, Dysport®, Xeomin®, and Prosigne. Although the toxin is the same, it is enfolded by different proteins which modify the relative potency of each brand. This was the basis for the introduction of the non-proprietary names onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA) and incobotulinum toxin A (incobotA) for Botox®, Dysport® and Xeomin®, respectively. Prosigne is the proprietary name of a BTX-A produced in China, which currently does not have a known non-proprietary name. Most of the information available about intravesical application of BTX-A derives from the use of onabotA (Botox®).

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Although potency of each toxin brand is expressed in units (U), the doses are not inter-changeable and conversion ratios between the different brands do not exist. Estimates from studies carried in the skeletal muscle suggest that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Nevertheless, these equivalences should be approached with caution [2–5].

In a study in the mice the capacity of 1 U of onabotA and 1 U of abobotA to cleave SNAP25 were compared after one single injection in the bladder wall. The conversion ratio between onabotA and abobotA was estimated around 1:1.6 [6].

33.2 BTX-A

BTX is synthesized as a single chain protein (150 kD) that is posteriorly cleaved in a heavy and a light chain linked by a disulphide bond. There are four A subtypes classified based on up to 15% variation in the amino acid composition. The amino acid sequence of the BTX-A light chain constitutes a catalytic Zn-dependent endopeptidase domain. The heavy chain is subdivided into three portions (HN, HCN, and HCC), but only two have clear functions. The HCC is associated both with the recognition of neuronal-specific areas and toxin internalization. The HN is responsible for translocation of the light chain from synaptic vesicles into the neuronal cytoplasm. In the synaptic cleft BTX-A binds predominately to the isoform C of the synaptic vesicle protein or SV2 (SV2C) [7, 8] or to the FGF receptor 3 [9] by the heavy chain.

After the binding of the toxin to SV2 it is internalized by the nerve terminal during the recycling process of synaptic vesicles. The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble N-ethylmaleimide sensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_33

(SNAP 25), synaptobrevin (vesicle associated membrane protein—VAMP) and syntaxin. BTX-A cleaves SNAP 25 rendering the SNARE complex inactive [1, 10]. Subtype B, acts preferentially through the inactivation of VAMP [10]. Inactive SNAP-25 (cleaved) appears rapidly after BTX-A injection. In the guinea-pig a robust expression of cleaved SNAP 25 could be detected already at 12 h and maximum intensity could be detected at 24 h. Almost all parasympathetic fibers, either preganglionic and postganglionic were affected while less than half of the sensory fibers express the cleaved protein [11, 12]. In neurogenic detrusor overactivity (NDO) patients, Schulte-Baukloh et al., detected cleaved SNAP 25 in the urinary bladder up to 11 months after BTX-A injection [13].

BTX-A application was extensively evaluated in striated muscle. In this tissue paralysis occurs by prevention of acetycholine (Ach) release from cholinergic motor nerve endings [10]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Striate muscle paralysis recovers within 2–4 months. During this time axons develop lateral sprouts and eventually regenerate completely [14].

SV2 and SNAP-25 are expressed in parasympathetic, sympathetic and sensory fibers in the human bladder [15]. The blockade of ACh release is believed to play an essential role in detrusor hypo- or acontractility that follows BTX-A injection in the bladder. In accordance with this view it was shown that in normal animals or with spinal cord injury (SCI) BTX-A treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering intrinsic contractions [16]. However cholinergic axon sprouting concomitant with clinical remission could not been documented in the detrusor [17].

Bladder sensory impairment is also expected to play an important role in the final effect of BTX-A bladder injection. About half of the peptidergic sensory fibers express SV2 and SNAP25 [15]. BTX-A has also been shown to reduce the suburothelium immunoreactivity for TRPV1 or P2X3 [18]. BTX-A also impedes TRPV1 trafficking from intracellular vesicles to the neuronal membrane, as this process is also dependent on SNARE proteins [19, 20].

Urothelial function seems also compromised after BTX-A administration. BTX-A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury [21, 22].

A decrease in the levels of Nerve Growth Factor (NGF) [23] and Brain-derived Neurotrophic Factor (BDNF) [24] in the bladder and/or urine following BTX-A injections may also contribute to the final effect of BTX-A in the urinary bladder, as both neurotrophins are relevant for growth, maintenance and plasticity of sensory nerves.

BTX-A has a unique long lasting effect, its duration in the detrusor smooth muscle being longer than in striated muscles. There is no firm explanation at the moment for the longevity of BTX-A activity. At least in part, it is given by the presence of two leucine amino-acids in the light-chain of the toxin which increases its resistance to degradation and therefore maintains the protease activity over the SNAP-25 for long periods of time [25]. The longer persistence of the light chain activity plus the involvement of pre and post- ganglionic parasympathetic neurons may therefore contribute to long persistence of the BTX-A effect in the bladder.

To date, there is no evidence that repeated injections of OnabotA into the detrusor muscle cause histologic alterations in bladder wall. No evidence of inflammatory infiltrates, fibrotic activity or apoptosis within the bladder wall were described [26, 27]. Rather the reverse, one study demonstrated that NDO patients treated with BTX-A had less fibrosis than nontreated patients [26].

33.3 BTX-A Injection Protocol in the Bladder Wall

Stohrer et al. reported in 1999 the first results with BTX-A injections into the bladder wall for NDO patients [28]. In 2000 Schurch et al. described the methodology: in this report, onabotA was diluted in normal saline in order to obtain a concentration of 10 U/mL [29]. Under visual control through a rigid cystoscope and a flexible 6 Fr injection needle, 30 injections of 1 mL (10 U of botulinum-A toxin) were done in 30 different bladder wall locations above the trigone to prevent vesico-uretheral reflux. Additional refinements have been added to this technique along the following years, including the use of a local anaesthetic agent (4% lidocaine) and a flexible cystoscope [30].

The pivotal studies [31, 32] which included more than 700 NDO patients led to the approval of a dose of onabotA 200 U applied in 30 injections sites above the trigone (1 mL saline each 6.66 U/mL). The studies showed that 300 U produced the same results and had the same duration of effect but caused more adverse events than the 200 U dose [31, 32].

Despite the existence of an approved protocol for OnabotA injection in the bladder wall, in NDO, several variations have been investigated and the suggested risks of ureteral reflux after injecting bladder trigone were never demonstrated, whether OnabotA or abobotA was used [24, 33, 34].

Another variable under investigation is the reduction of injection sites while increasing the dose in each site. One study randomized NDO patients to receive 300 U either in 10 or 30 sites [35]. The authors reported that 10 site injection was quicker and less painful and that no differences in efficacy between the two procedures could be detected up to 24 weeks. In another study it was found that patients receiving 300 U of onabotA distributed over 30 injection sites

(30 mL of fluid in total) or the same dose of toxin distributed over 10 injection sites (10 mL of fluid in total) had a similar distribution of the fluid, as determined by MRI. About 1/3–1/4 of the total detrusor volume was covered by the two protocols, respectively [36].

Another variation is the volume of the saline used to reconstitute the toxin. Most studies used 1.0 mL per injection, although a few used 0.5 mL [37], 0.2 mL [38], 0.25 mL [39] or even 0.1 mL per injection site [40]. However control studies designed to compare different number and locals of injection and the volume of each injection are necessary.

AbobotA administration remains off-label. Nevertheless, in larger cohorts coming from several institutions aboboatA was applied in the bladder wall by similar technique albeit the number of injections was only 20 [39, 41]. A total of 500–1000 U of abobotA are injected [41]. The volume of saline at each injection site is commonly 1 mL but volumes so low as 0.25 mL per site were also used [39]. At the moment of writing this chapter, large randomised phase III placebo controlled trial investigating two different doses of abobotA, 500 or 800 U in NDO patients is ongoing.

The importance of antibiotic prophylaxix before botulinum toxin injection in SCI patients on clean intermittent catheterization (CIC) was investigated in 154 patients undergoing a total of 273 treatment cycles with onabotA. Patients with no clinical signs of urinary tract infection (UTI) underwent injections without antibiotic prophylaxis. Symptomatic UTI occurred in 7% (5/73) of cases with sterile urine culture and in 5% (9/200) with bacteriuria. These results suggest that routine antibiotic prophylaxis may be dispensable prior to BTX injection in assymptomatic SCI patients on a CIC programme [42].

33.3.1 Effect of BTX-A on NDO Adult Patients

33.3.1.1 OnabotA

Two large pivotal phase 3 studies where efficacy and safety of Onabot A 200 and 300 U were studied in about 700 patients with urinary incontinence due to NDO and urinary incontinence caused by multiple sclerosis (EDSS $\leq$ 6.5) or spinal cord injury below T1 [31, 32] led to the approval of OnabotA 200 U by FDA and by European Authorities in ND patients patients. Doses of OnabotA below 200 U were tested in patients with SCI below T1 and are less effective. No effect was observed in patients treated with 50 U [43].

In the two pivotal trials two doses, 200 and 300 U of onabotA were compared against placebo. Primary outcome measure was the change from baseline in week episodes of urinary incontinence at week 6 after treatment. Secondary outcome measures included the change from baseline in maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction and quality of life using the I-QOL total score. Both studies yielded similar findings, and indicated that 200 and 300 U provided the same effect and had the same duration of action. In the first study [31] onabotulinumtoxinA significantly reduced UI and improved QOL in both MS and SCI patients, with no clinically relevant differences between the two doses. At week 6 mean change from baseline in weekly incontinence episodes was −21.8 in onabotA 200 U, −19.4 with 300 U and −13.2 with placebo ($p < 0.01$). At the same time point 7.6%, 38.0%, and 39.6% of patients in the placebo, 200 U, and 300 U OnabotA groups, respectively, were fully continent. The proportion of patients without IDC was around 60% after OnabotA 200 and 300 groups but only 17.4% after placebo. In the second study [32], OnabotA resulted in a 23.0%, 26.7% and 27.4% change from baseline in the incontinence episodes in the placebo, and 200 and 300 groups, respectively. Furthermore, 36% and 41% of patients in the 200 and 300 U groups, respectively, achieved dry status, contrasting with 10% in the placebo arm. In both studies, detrusor pressure and cystometric capacity increased significantly with the two onabotA doses, without clinically relevant differences between them [31, 32]. Patients could request a retreatment 12 weeks after initial treatment. Median time for saline treated patients was about 90 days and 250–300 days for those treated with 200 or 300 OnabotA, without differences between the two doses [30, 31]. No differences were found between patients with SCI or MS in terms of clinical response to OnabotA [31, 32].

The symptomatic improvement induced by intravesical BTX-A injection does not correspond to the moment of injection. However, in the pivotal trials, significant decrease in the number of incontinence episodes over placebo were already detected at week 2 after injection [31, 32].

In a pooled data analysis by etiology in 2013, by Ginsberg et al., both MS and SCI patients treated with OnabotA exhibited decreases from baseline in urinary incontinence episodes that were significantly larger than those treated with placebo. A significantly higher percentage of MS and SCI patients were dry during week 6 after treatment than in the placebo group. The change in the number of voluntary voids per week was examined only in MS patients, the majority of whom did not use intermittent self-catheterization at study entrance. Following onabotA 200 U treatment, a decrease from baseline of two micturitions per day at week 6 and around three micturitions per day at week 12 was detected [44]. There was no difference in terms of continence between patients on or off anticholinergic medication [44].

As a consequence of the symptomatic improvement detected after onabotulinumtoxinA injection, NDO patients of both MS and SCI etiologies found a significant improvement in quality of life [32, 44, 45]. The change from baseline in I-QOL score was analyzed in patients who did not perform CIC at baseline. Surprisingly, the magnitude of the

I-QoL improvement was similar whether they did or did not require CIC after toxin administration [32].

In the recent subanalysis of the pooled data of the two pivotal studies, about 60% of the patients were taking anti-muscarinics and maintained the same dose. Data showed that the proportion of patients fully dry and reductions in urinary incontinence episodes were similar, regardless of anti-cholinergic use. The median time to patient request for re-treatment were similar in anti-cholinergic users and non-users, as well [44, 46].

BTX-A treatment in NDO patients decrease the incidence of severe urinary tract infections. In 30 SCI patients Gamé et al. [47] observed that the number of pyelonephritis, orchitis and prostatitis in the 6 month before OnabotA 300 U, 1.75 ± 1.87 per patient, decreased to 0.2 ± 0.41 in the first 6 month after treatment. In 17 SCI patients that received OnabotA injections for a period of 6 years, the number of urinary tract infection at the sixth year was 1.8 ± 0.5 per year, much lower lower than 6.7 ± 2.1 episodes per year before treatment [48]. In a multicentre, cross-sectional retrospective cohort study of 214 NDO patients treated in seven German centers the rate of urinary tract infections in 12 months preceding and in the 12 months following OnabotA was 68% and 28%, respectively [49].

Multiple Sclerosis patients represent a particular subgroup of patients in whom a careful analysis of the efficacy and safety of BTX-A requires additional attention if voluntary voiding is present before treatment. The first cohort studies used OnabotA 300 U and while this dose was effective in improving or curing urinary incontinence most patients non-catheterizing at baseline had to initiate CIC [50, 51]. In spite of this drawback, improvements in quality of life were quite remarkable indicating that patients may prefer CIC to incontinence [50, 51]. The large pivotal phase 3 studies [31, 32] showed that 200 and 300 U of onabotA had exactly the same efficacy in terms of continence and duration of effect but 200 U had a much lower risk of urinary retention and de novo CIC.

The efficacy and safety of 100 U of OnabotA in MS patients non-catheterising before OnabotA injection was recently compared against placebo. Injections of 1 mL each were carried out in 30 places above the trigone containing onabotA (n = 66) or saline (n = 78). OnabotA 200 U significantly improved UI episodes/day compared with placebo (−3.3 vs −1.1; P < 0.001), and improved all the key urodynamic parameters like maximal cystometric capacity and maximal detrusor pressure. Improvements in I-QOL total score with onabotA were 4 times higher than placebo (40.4 vs 9.9; P < 0.001). Median duration of effect was 11.9 for OnabotA and 2.9 months for placebo (P < 0.001). The risk of UTI (25.8%) and de novo CIC (15.2%) after 100 U OnabotA was half of that observed with 200 U of toxin injections [52]. This RCT confirmed therefore the small pilot studies that had reported successful results with OnabotA 100 U in non-catheterising MS patients [53].

From the initial pivotal trials it was possible to conclude that there is no risk of MS exacerbation after onabotA administration. The annualized event rate was 0.36 and 0.19 in the onabotA and placebo populations, respectively, clearly in the lower range of the annualized rate known for the general MS population, between 0.2 and 1.2 [54].

33.3.1.2 AbobotA

AbobotA is not officially approved for NDO and has been the object of investigation in a few comparative clinical trials. A small study randomized a total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of abobotA 500 U or placebo [55]. Patients in the abobotA arm had a significantly higher cystometric capacity at 6 and 12 weeks, lower maximum detrusor pressure and episodes of urinary incontinence and less consumption of anti-muscarinic drugs. Efficacy and safety of abototA were, additionally, investigated in NDO patients that had abandoned anticholinergic therapy. Two doses, 500 U (n = 39) or 750 U (n = 38) were compared. Complete continence at day 30 was observed in 22 patients (56.4%) and 28 patients (73.7%) receiving 500 U or 750 U, respectively. The median delay in the reappearance of leakages was 168 days. Although there was a trend towards a greater improvement with 750 U, no statistically significant differences in terms of clinical and urodynamic variables and QoL were found between the treatment groups. Excellent tolerability was reported for both doses [39].

A single-center retrospective study investigated 750 U intradetrusor injection of abobotA in 81 consecutive patients performing CIC. Six weeks after the first injection, the success rate, defined as a combination of no incontinence episode, a number of catheterization <8 reported in a 3-day bladder diary and the lack of detrusor overactivity, was reported in 64.2%. Mean reinjection number was 3.9 and mean interval between reinjection was 8.8 ± 3 months. The clinical efficacy rate after each reinjection (up to 14) was at least 86.7% [56].

Recently a phase IIa, randomised, placebo controlled, pilot study enrolled 47 patients with NDO and urinary incontinence resulting from spinal cord injury (SCI) or multiple sclerosis (MS). Patients were treated with 15 intra-detrusor injections of abobotA 750 U or the equivalent placebo (n = 16 and 7) or 30 injections of abobotA 750 U or the equivalent placebo (n = 17 and 7). Primary endpoint was change from baseline in mean number of daily incontinence episode frequency at day 84. Adjusted mean changes from baseline were −3.2 and −1.7 in the 15 injections group for abobotA and placebo, respectively. In the 30 injections group the change was −3.2 and −2.6, respectively for the toxin and

placebo. Statistically significant improvements in maximum cystometric capacity, maximum detrusor pressure and volume at first contraction were reported in the toxin groups compared with placebo [57].

33.3.2 Adverse Events in NDO Patients After BTX-A Injection

The most common adverse events in NDO patients after BTX-A injection were UTI and de novo CIC [32, 33, 44].

In the SCI population, the majority of which was performing CIC at baseline, the incidence of UTI was similar across all treatment groups (around 50%). In the MS population, the rate of UTI was highest in the onabotA 300 U arm (saline 32%, 200 U: 58.5%, 300 U: 70%) observed in the study by Cruz et al. [32] whereas the incidence of UTI was similar, around 50%, after 200 and 300 onabotA doses in the study by Ginsberg et al. [33]. The high incidence of UTI among MS patients in the pivotal studies was related with dose dependent increase in PVR and necessity of de novo CIC. The latter was considered necessary in 12.2% of the patients after saline, 29.5 after 200 U, and 42.2 after 300 U in the study by Cruz et al. in 2011. On the other hand Ginsberg et al. [33] observed that the incidence of de novo CIC in patients not catheterizing at baseline was dose dependent 10% on placebo, 35% on 200 U and 42% on 300 U, and also mainly affected MS patients. The pooled data of the two pivotal studies showed that the incidence of UTIs was similar among all treatment groups for SCI patients ($P = 0.534$), but was higher in the onabotA-treated MS patients compared with placebo ($P < 0.001$). However, very few complicated UTIs were reported: pyelonephritis was reported in one MS patient (onabotulinumtoxinA 300 U group) and in two SCI patients (both in the placebo group), and urosepsis was reported in two SCI patients (both in the placebo group). Among patients non catheterizing at baseline that received 200 U of onabotA about 1/3 required CIC. The period of time in which CIC was required was long lasting (>36 weeks) in about half of them [44].

Data from long-term studies that followed the large RCT are now available. In NDO, most common adverse events during 4 years follow-up were urinary tract infections and urinary retention. De novo CIC rates were 29.5%, 3.4%, and 6.0% (200 U), and 43.0%, 15.0%, and 4.8% (300 U) for treatments 1–3, respectively; de novo CIC rates were 0% for treatments 4–6 [58]. UTI ranged between 20% and 30% along the follow-up without relevant differences bewteen patients treated with 200 U or 300 U [58].

The risk of urinary retention and de novo CIC in MS patients non-catheterising before treatment may be substantially decreased by using a lower dose of the toxin. Using 100 U of OnabotA in non-catheterising MS patients de novo CIC (15.2%) and the rate of UTI (25.8%) was half of that observed with 200 U of toxin injections [52]. At this moment it is not possible to identify beforehand patients who will develop voiding difficulties after BTX-A injection.

Episodes of autonomic dysreflexia in SCI patients during injection were rare. Cruz et al. [32] reported two cases in 183 injected with the toxin. Ginsberg et al. [33] in 167 injected patients reported seven events of autonomic dysreflexia. Hematuria may occur after the toxin injection but in most of the times is mild in nature and does not require any active treatment.

Antibody formation against OnabotA were not detected in the pivotal RCT during the first treatment cycle [32, 33].

Transient muscle weakness is a rare event after BTX-A injection in the bladder. Nevertheless, caution should be used in selecting high risk patients for botulism including children, patients with low pulmonary reserve or patients with myasthenia gravis. Aminoglycosides should be avoided during BTX-A treatment since they might blockade motor plates and therefore enhance BTX-A effect. Cruz et al. [32], among 183 patients treated with OnabotA 200 U or 300 U reported only one case of muscular weakness in an SCI patient treated with onabotulinumtoxinA 300 U. Among 199 NDO patients treated ith abobotA during 8 years, five developed hypostenia when injected with abotbotA 1000 U [41]. In another study with 44 patients, three adults also treated with 1000 U developed muscular weakness which subsided after 5–7 weeks [59]. In a recent phase IIa RCT with abobotA 750 U, three cases of muscle weakness episodes were reported in two tetraplegic and one paraplegic patient among 15 NDO patients who received the toxin in 15 injection sites [57].

33.3.3 BTX-A in Children

The dose of BTX-A in children should be calculated according to body weight. Doses of 12 U/kg of weight up to a maximum dose of 300 U [60] and 4 U/kg have been used for onabotA. The maximum suggested for abobotA is 20 U/kg up to a maximum of 400 U [59, 61]. BTX-A has been essentially assayed in children with myelomeningocele [60–64]. Similar to adults, the toxin increased bladder capacity and decreased maximal detrusor pressure. In 26 children with a mean age of 6.9 years, 19 of them (73%) became completely dry between clean intermittent catheterizations while 88% reported a global improvement in urine incontinence. Interestingly, in 11 (73%) out of the 15 children who had vesicoureteral reflux before injection, reflux either disappeared or decreased in grade. BTX-A also improved bowel function in 66% of the children with intestinal problems [64]. The success rate in terms of continence and cessation of anticholinergic medication may, however, be substantially inferior to that seen in adults, potentially due to irreversible

bladder wall changes associated with longstanding detrusor overactivity [61]. In a group of 20 children with myelomenigocele continence was achieved in only 13 children. At a second injection, this number also did not change appreciably [61]. A recent systematic review found a total of 13 studies reported on 368 children receiving BTX-A for NDO, none with a placebo comparator arm. The only parameters reported with consistency between studies were the MCC and MDP, which changed by between 42 and 59% [65].

Electromotive administration of BoNT/A may represent a substantial breakthrough among children. In 15 children with NDO due to myelomeningocele, electromotive administration of abobotA instilled in the bladder in a dose of 10 U/kg, proved very effective and safe. The mean reflex volume (99 ± 35–216 ± 35 mL) and maximal bladder capacity (121 ± 39–262 ± 41 mL) increased substantially while maximal detrusor pressure decreased from 75 ± 16 to 39 ± 10 cm H2O. Urinary incontinence improved in 12 patients (80%) [66].

33.4 BTX-A Injection in Urethral Sphincter

BTX-A injection in urethral sphincter was reported for the first time in 1988, thus before the report of bladder injection, by Dykstra et al., who treated 11 male patients with SCI and detrusor sphincter dyssynergia (DSD) [67]. Posteriorly other indications were added like chronic urinary retention due to Fowler's syndrome, detrusor underactivity after pelvic surgery, pelvic floor spasticity and idiopathic voiding dysfunction. The objective of BTX-A injection in the sphincter is to reduce the strength of its contraction, and allow spontaneous voiding. In many patients this treatment will reduce or avoid the necessity to perform clean intermittent self-catheterization to empty the bladder or avoid a permanent indwelling urethral or suprapubic catheter. In patients with DSD toxin injection in the sphincter may avoid the permanent external sphincterotomy and appliance of penile sheaths to contain subsequent incontinence.

In the studies reported, BTX-A has been administered by transperineal or transurethral injection.

Doses injected were between 50 and 200 U, although the majority of studies evaluating BONT/A in DSD have used a dose of 100 U [68]. The largest placebo controlled study was conducted by Gallien et al. and included 86 patients with multiple sclerosis (MS) and DSD. Patients were randomized into either BTX-A 100 U or 0.9% saline, with treatment administered through a single transperineal injection using sphincter EMG guidance, it was observed that in the treatment arm, patients did have significant increased voided volumes (+54%, P = 0.02) and lower maximal detrusor pressures (−21%, P = 0.02) [69].

The most recent study about injection of BTX-A in urethral sphincter was reported by Yang et al. [70], in this work, 15 patients with DSD secondary to SCI were injected with 100 U of BONT/A via TRUS guided transurethral injection in external urethral sphincter and 76% of the patients showed improved or excellent results [70].

In general, most studies in DSD, suggest that after injection there is a reduction in voiding pressure, a reduction in PVR volumes and reduced maximal urethral pressures, which would demonstrate a reduction in urethral resistance, with duration of effect ranging between 3 and 9 months. No serious adverse events were attributable to BTX-A injection in the sphincter, with the exception of a mild transient stress urinary incontinence [68].

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Botulinum Toxin and the Bladder: Future Research Directions

34

Apostolos Apostolidis

34.1 Introduction

As the method for intradetrusor injections of BoNT/A has not been standardised yet for maximization of efficacy and safety and while the injection technique remains minimally invasive with some assorted patient discomfort and potential transient complications from the injections [1], several injection-free techniques have or are being tested in preclinical and clinical studies [2]. Plain intravesical instillation of BoNT/A, intravesical delivery of BoNT/A via electromotive-drug administration or following bladder treatment with protamine sulphate or low-energy shock-waves, instillation of BoNT/A mixed with dimethyl sulfoxide (DMSO), conjugated with liposomes or cationic peptides and complexed with thermosensitive hydrogel are some of the novel techniques under investigation [2]. Almost all techniques aim at increasing the toxin's permeability via the urothelium.

34.2 Injection-Free Delivery of BoNT/A into the Bladder

34.2.1 Plain Intravesical Instillation of BoNT/A

In a rat model of BOO-induced DO, intravesical instillation of 5 U of BoNT-A produced similar significant decreases in the average intermicturition and threshold pressures, as well as the number and amplitude of non-voiding bladder contractions as the bladder wall injection of the same dose in conscious cystometrograms performed 7 days and 2 weeks after treatment. Interestingly, no effect was shown on the micturition pressure in the intravesical instillation group as opposed to the injection group [3]. A pilot study from the same group of researchers using simple intravesical instillation of 200 U OnaBotA in 50 mL of 0.9% saline had reported significant improvement in the average number of incontinence episodes and the volume at first non-voiding contraction which increased by 52.8% in 7 out of 16 OAB-wet women 1 (one) month after treatment [3].

Interestingly, intravesical instillation of BoNT/A in a rat cystitis model produced significant decreases in the bladder inflammatory reaction, the expression of cyclooxygenase-2 and prostaglandin-2 receptor EP4 in the bladder and spinal cord, and improved bladder overactivity via a significant increase in intercontraction intervals [4]. No human study has confirmed such findings to-date.

34.2.2 Elecromotive Drug Administration + BoNT/A

The method involves the placement of an electrode via a catheter in the bladder and one on the abdomen, and achieves increase of urothelial permeability via a combination of iontophoresis, electroosmosis and electroporosis. To date, it is the only injection-free technique with published results in patients with neurogenic detrusor overactivity, namely children with myelomeningocele. In a small, pilot study 10 IU/kg of AbobotulinumtoxinA (Dysport®) was delivered to the bladder of 15 patients aged 3–16 years, while a pulsed current generator delivered 10 mA for 20 min. The authors reported significant urodynamic improvements in maximum cystometric capacity (MCC) (+116%), max. Detrusor pressure (Pdetmax) and end-fill pressure (−48% and −41%, respectively), as well as in urinary incontinence (−80%) and vesicoureteral reflux (improved in 58% of patients) and fecal incontinence (improved in 83% of patients) [5]. A long-term follow-up study of 24 patients by the same group of researchers reports that 18/24 (75%), 11/24 (45.5%), 9/24 (37.5%), 8/24 (33%) and 7/24 (29.1%) of the patients were completely dry between two consecutive clean intermittent catheterizations after once BoNTA/EMDA treatment at 1, 2, 3, 5 and

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6 years of follow up respectively [6], with concomitant improvements in MCC and Pdetmax.

34.2.3 DMSO + BoNT/A

Animal studies have shown that bladder instillation of DMSO increases the permeability of the urothelium to a variety of agents [7]. In an animal model of interstitial cystitis the combination of BoNT/A with DMSO exerted a protective role against the irritative effect of acetic acid (short report) [8]. A single human study to-date explored the efficacy and safety of this combination. Three hundred units of OnaBotA mixed with 50 mL of 50% DMSO were administered intravesically in 22 women with idiopathic OAB, producing significant improvements in the number of urgency incontinence episodes and the scores of the UDI-6 and IIQ-7 questionnaires but only for up to 1 month post-treatment [9]. No improvements were noted at 3 months. No studies in neurogenic bladder have been published to date.

34.2.4 Protamine Sulfate and Protein Transduction Domains

Bladder instillation of protamine—a cationic peptide which crosses membranes via protein transduction—at specific concentrations may result in denudation of the urothelium, rendering it permeable to various agents, including onaBotA. Protein parts that facilitate transduction are called protein transduction domains (PTDs) and are thought to be able to link to OnaBotA allowing a receptor-independent translocation via the cell membranes.

To date, pre-treatment of the bladder with protamine sulfate has been used effectively in a rat model of spinal cord injury, where bladder function was only affected in rats receiving protamine before intravesical OnaBotA [10]. No available studies exist for the use of PTDs for delivery of BoNT/A into the bladder. However, PTDs have been used for the transdermal delivery of BoNT/A via a gel application for the improvement of wrinkles in a human study [11].

34.2.5 Liposome-Encapsulated Toxin (Lipotoxin)

The constitution of liposomes—an aqueous core surrounded by phospholipid bilayer—allows them to encapsulate hydrophilic and hydrophobic molecules, which can then be delivered to cells via endocytosis [12]. Interest in fusion of BoNT/A with liposomes has been ongoing for three decades now [13–15]. It has been shown that following liposomal encapsulation the light chain of BoNT/A remains active, when delivered in motor nerve endings [15]. In addition, in vitro experiments using cultured urothelial cells provided evidence for a protective role of liposomes on the cells, increasing their survival against 'toxic' agents, such as acrolein [16]. Further experiments demonstrated the cleavage of SNAP25 by liposome-encapsulated BoNT/A in the urothelium as well as its inhibitory effect on the release of neurotransmitters (see review by [17]).

Two randomized placebo-controlled studies examined the effect of the intravesical delivery of liposome-encapsulated BoNT/A in 24 and 55 patients, respectively, with non-neurogenic OAB refractory to antimuscarinics [18, 19]. Both studies demonstrated a short-lived effect of the 'lipotoxin' on frequency and urgency episodes for up to 1-month post-treatment. The latter study also found significant improvement in patient-reported outcomes (OABSS, USS, Global Response Assessment questionnaires) only in the lipotoxin-treated group but the positive effect could not be sustained until week 12 (end-of-study visit). In addition, no significant change was seen in urgency incontinence episodes. The authors reported also none of the common adverse events recorded in the studies of bladder-injected BoNT/A, such as urinary retention or urinary tract infections, speculating a urothelial but not a detrusor effect of this alternative delivery method [19]. These results may be in alignment with finding from preclinical urodynamic studies, where lipotoxin instillation had a partly protective effect against the affect of acetic acid on intercontraction intervals, without affecting voiding function. The lipotoxin appeared to also have a better outcome regarding histological inflammation and urothelial sensory neuropeptide release than the instillation of either empty liposomes or BoNT/A alone [20].

Intravesical administration of liposomes was also found to be equally if not more effective than DMSO in a pilot randomized study of patients with IC/BPS for up to 8 weeks [21]. In addition to improvements in frequency and nocturia, significant decreases in the O'Leary-Sant symptom index, pain and urgency were only seen in the liposome group. Similarly, improvements in urgency for up to 12 weeks and pain for up to 8 weeks were seen in a small open-label study of 14 patients with IC/BPS treated with liposomes alone [22]. Despite these encouraging results, a 2-centre double-blind, placebo-controlled trial in 59 IC/BPS patients failed to show better improvements in symptom scores with intravesical administration of 'lipotoxin' (onaBotA 200 U + sphingomyelin 80 mg) compared to either onaBotA or placebo alone [23].

34.2.6 Thermosensitive Hydrogel and BoNT/A

Thermosensitive hydrogels are temperature-dependent aqueous solutions of polymers, which are used to increase the

time of drugs in the bladder when instilled intravesically. They are liquid upon instillation, but become semisolid when in body temperature. Embedment of BoNT/A in hydrogels appears to prolong the intravesical release of BoNT/A for up to 6–8 h as opposed to the 2 h produced by a simple instillation [24]. Two small studies have investigated the intravesical delivery of BoNT/A embedded in hydrogel. A pilot, randomized, double-blind study of women with idiopathic OAB using 200 U OnaBotA embedded in inert TC-3 hydrogel delivered via intravesical instillation in comparison to placebo, combination with DMSO or DMSO alone showed superiority of OnaBotA + hydrogel over the other delivery methods in the number of urgency episodes/72 h, number of leakage episodes/72 h, Overactive Bladder Questionnaire total score and Patient Perception of Bladder Condition total score when using alternative statistical analysis methods [25]. Another pilot study investigated OnaBotA + hydrogel versus plain OnaBotA instillation in 15 women with BPS/IC, with efficacy and safety examined at 3 months post-treatment by the Interstitial Cystitis Symptom Problem Index and visual analog score [24]. Results were promising enough to probe further clinical testing.

34.2.7 Low-Energy Shock Waves (LESW)

Shock waves delivered to the bladder are thought to increase urothelial permeability by causing shear forces via movement of liquids relative to cells [2]. In contrast to increasing number of human studies investigating LESW for erectile dysfunction and male pelvic pain syndrome, their use in the bladder has only been tested in preclinical studies. In a rat model of IC/BPS, Chuang et al. demonstrated the increased urothelial permeability following LESW using magnetic resonance imaging with a contrast medium and consequently found that onaBotA delivered via LESW could ameliorate the decrease in intercontraction intervals and reduce inflammation as well as the levels of SNAP-25 and COX-2 [26]. In a model of diabetic bladder dysfunction, LESW alone could improve bladder function via recruitment of endogenous stem cells resulting in increased release of nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) and thus improving bladder innervation and vascularization [27].

34.3 New Toxin Forms

Modifications of the toxin's molecule are already under investigation as novel therapeutic options in a variety of fields, possibly including Urology. Modification of the residues included in the binding domains of the heavy chains of botulinum neurotoxins (BoNTs) may enhance their binding, uptake and toxicity. Modification of the binding domain may also aim at altering the neuronal specificity of binding allowing the delivery of the catalytic domain into non-neuronal cells. Other experimental forms are chimeric proteins which combine characteristics of various BoNTs, allowing modulation of targets which were otherwise resistant to both parent toxins. Novel therapeutic conjugates have been created between the light chain catalytic domain of BoNTs and the binding domains of non-toxic proteins, allowing again retargeting of cells otherwise refractory to the toxin's action. The latter two techniques have already been tested in vivo for sensory neuromodulation in pain conditions. Other chimeric conjugates have been developed to exploit the binding properties of BoNTs in order to deliver active, non-native proteins to cells, after removal or inactivation of the active catalytic light-chain domain of the various BoNTs. Further to their use as vehicles for small molecule drugs, such chimeric products can be used for the delivery of tracer proteins allowing the mapping of neuronal circuits in various disease conditions. Finally, other modifications allow BoNTs to target different substrates from their native ones or alter their duration of action [28].

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Balloon Dilatation

35

David Manuel Castro-Diaz and Barbara Padilla-Fernandez

In addition to its use in the setting of bladder outlet obstruction due to BPH, balloon dilatation has been proposed as a potential approach for the management of detrusor external sphincter dyssynergia [1]. Indeed, some believe this procedure represents a technically-simpler approach than a complete surgical sphincterotomy, with less chance for blood loss or other associated complications.

This technique was first described by Chancellor et al. in 1992, who report their experience with a cohort of seven spinal cord injured men. They begin with cystoscopy to evaluate the sphincter and rule out bladder abnormalities. Next, a guidewire is passed via the cystoscope, and a prostate balloon dilatation catheter is inserted over the wire into the bladder. Fluoroscopy is employed to guide positioning, with the positioning balloon first inflated in the prostatic urethra, then pulled back until it sits 1–2 cm distal to the external sphincter. The dilatation balloon is then gradually inflated with the external sphincter at its midpoint. With the balloon properly positioned across the external sphincter, a waist will be seen, which will 'pop' or disappear as the balloon is inflated to 4 atm pressure. The inflated balloon is left in place for 10 min, and then removed. A 22 Fr three-way Foley catheter is inserted, and a retrograde urethrogram performed to assess for extravasation. Typically, this reveals a small amount of extravasation from multiple tears in the external sphincter.

If the urine is bloody, continuous bladder irrigation may be initiated. Otherwise, the catheter is left to straight drain. The patient is typically discharged after a 24–48 h, and the catheter removed in approximately one week. In Chancellor's group of seven men, varying in age from 21 to 39 years and requiring catheter drainage of their bladders prior to balloon dilatation, all subjects were successfully voiding post-operatively, without dribbling incontinence or diminishment of renal function at four months follow-up. Symptoms of autonomic dysreflexia improved in all patients. One man did develop delayed post-operative bleeding and required transfusion.

There have been several well-designed studies comparing the effectiveness and complications of balloon dilatation versus conventional external sphincterotomy in the treatment of DESD. After their initial description of the procedure, Chancellor and colleagues compared balloon dilatation to 12 o'clock sphincterotomy and Urolume endourethral stent placement [2]. This study was not randomized, and there were substantial differences in baseline characteristics between groups. However, the results suggested that both balloon dilatation and stenting were comparable with sphincterotomy in terms of frequency of post-procedural febrile UTIs (15–20%) and resolution of hydronephrosis (50–100%) over 12 months follow up. Complications of balloon dilatation in this study (20 subjects in this arm) included blood transfusion (5%), bulbar urethral stricture (5%), and recurrent obstruction (15%). None of the patient's treated with balloon dilatation noted decreased erectile function. PVRs and maximum voiding pressures were similar across groups at 12 months (33–67 mL and 27–36 cm H_2O).

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_35

Part XI

Electrical Stimulation and Neuromodulation

Sacral Deafferentation and Anterior Root Stimulation: The Brindley Procedure

36

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36.1 Introduction

After years of research and experimenting, neurostimulation of the sacral anterior roots (S.A.R.S) in humans, was introduced by Giles S. Brindley from London in the early 1970s. He aimed at restoring evacuation of urine in patients with neurogenic bladder dysfunction due to spinal cord injury by electrical stimulation of the sacral nerves (S2–S4). By selective stimulation of these sacral roots, micturition was induced by detrusor contraction. Together with the company Finetech Ltd. a silicon embedded implant was developed that consisted of an array of electrodes, connected to a subcutaneous receiver that could be stimulated by electromagnetic transmission from an external transmitter [1, 2]. The first implant was performed in a human in 1976 [3]. However, at that moment the treatment did not address the problem of detrusor contractions and incontinence between episodes of micturition. Later, Brindley together with D. Sauerwein from Bad Wildungen combined the implantation of the electrodes with posterior rhizotomies at the S2–S4 levels. These rhizotomies result in a deafferentation as the sacral reflex arch (SDAF) is interrupted hence abolishing the reflex contractions of the bladder at low filling. Hence urinary incontinence is abolished and bladder capacity and compliance increase significantly. The combination of sacral anterior root stimulation using the Brindley stimulator and posterior rhizotomy has become known as the Brindley procedure [3, 4].

36.2 Indications

Normal bladder function depends on the integrity of central and peripheral nerve circuitry [5]. This reflex system will be disrupted after spinal cord injury (SCI), leading to different problems in bladder function. The type of lower urinary tract dysfunction depends on the grade and level of the lesion. In supra sacral lesions detrusor-overactivity (DO) and detrusor-sphincter dyssynergia (DSD) are typical urodynamics patterns and are associated with high upper urinary tract deterioration risk [6]. Different therapeutics strategies, including oral medication and botulinum toxin A injections may be effective for restoring the storage function but yield significant amelioration in only about 70% of the patients [7]. For those patients who do not respond adequately to conservative treatments of the detrusor overactivity, sacral deafferentation eventually in combination with the implantation of a sacral anterior root stimulator (SARS) may be a suitable alternative to other irreversible procedures such as augmentation cystoplasty or urinary diversion [8].

From a purely medical perspective, SDAF is indicated in patients with or at risk of:

- Autonomic dysreflexia
- Renal failure
- Urinary incontinence
- Recurrent urinary tract infections
- Difficult or traumatic bladder catheterization
- Failure of conservative bladder management with persistent low compliance
- Failure of conservative therapy because of unacceptable side effects.

From the point of view of bladder function the requirements for a posterior rizothomy and SARS implantation are:

- Motor and sensory complete spinal cord lesion (informed consent should be obtained as loss of sensation in the segments S2–S5 will occur)
- Patients with paraplegia van be candidate if the lesion is non-progressive or very slowly progressive.
- Intact spinal reflex arcs in the S2–S4 segments.

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- Intact detrusor function (no organic fixed fibrosis, no acontractility because of overdistension).
- Security of a long term therapeutic program for the spinal cord injured patient.
- Support and understanding of family and friends given the irreversible nature of the rhizotomies with in male patients loss of reflex erections [9].

Advantages of the dorsal rizothomies include: detrusor areflexia which provides continence, significant increase in bladder capacity and compliance, correction of detrusor-sphincter dyssynergia and abolishment of autonomic dysreflexic attacks triggered from the bladder and rectum.

However section of all six of the S2–S4 posterior roots abolishes reflex erection. Also genital sensation and reflex ejaculation is lost if these were present, and the patient must be informed of these consequences.

The SDAF and SARS implantation is contraindicated for patients with the following characteristics:

- Poor or inadequate bladder reflexes
- Active or recurrent pressure ulcers
- Active sepsis
- Implanted cardiac pacemaker
- Not fully matured skeletal structure

36.3 Mechanism of Action

During his first experiments, Brindley noticed that the external sphincter consists of striated muscles that tend to relax much faster than detrusor smooth muscle. Based on these differential responses, he stimulated ventral sacral nerve roots in paraplegic baboons (with bursts of 12 pulses/s lasting 100 ms, repeated every 1.5 s) to achieve sustained maximal detrusor contraction and intermittent contraction and relaxation of the external sphincter. This form of stimulation resulted in micturition in between the intermittent contractions of the external sphincter and achieved good bladder emptying [2]. This so called "post-stimulus voiding" is characterised by an intermittent stimulation pattern that allows the urethral sphincter to relax while the detrusor pressure remains elevated. The result is an intermittent flow pattern till complete evacuation of urine.

The stimulator consists in two different subsystems: the implanted components include the implanted receiver and either extradural or intrathecal electrode assemblies and the external components which include the controller, transmitter block, transmitter lead and battery charger. This implant is a radiofrequency powered motor control neuroprosthesis. When the transmitter block is positioned over the receiver, the external part sends radiofrequency signals that induce an electrical current in the implanted part.

36.4 Description of the Technique

Different approaches have been described to perform the rhizotomies and the electrode implant, the main ones being the intradural and extradural technique. Combined approaches (intradural rhizotomies and extradural electrode placement) have been described but are not frequently used.

During the intradural implant the implantation of the neurostimulator is performed in conjunction with posterior sacral rhizotomies. A median laminectomy from L4 to S2 is performed in order to allow for the posterior rhizotomies and the implantation of the intrathecal electrode book. The main advantage of the intradural technique as compared to the extradural technique is the lower risk of motor nerve damage, since it is easier to identify the sensory fibres and to separate them from the motor roots during the rhizotomy. However the intradural technique entails an increased risk of cerebrospinal fluid leakage.

In the extradural technique both, the posterior rhizotomies and the electrode implantation are performed on the extradural part of the sacral nerves through a laminectomy at the level of S1–S3. Removal of the L5 spinous process may facilitate the implantation of electrodes on the S2 roots by providing more room for the electrodes and routing of the cables. A potential disadvantage of this technique is the higher risk of anterior root damage and incomplete deafferentation [10, 11]. However, some authors have recently reported similar results with extradural approach without comparatively higher rates of motor injury or incomplete rhizotomies [12] (Figs. 36.1, 36.2, 36.3 and 36.4) (Table 36.1).

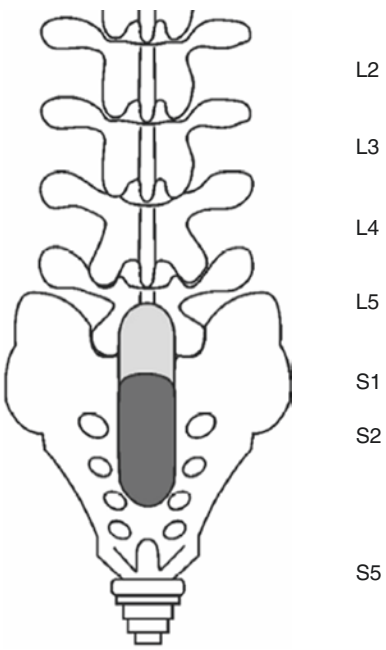

Fig. 36.1 The extradural approach (taken from Finetech Med programming manual)

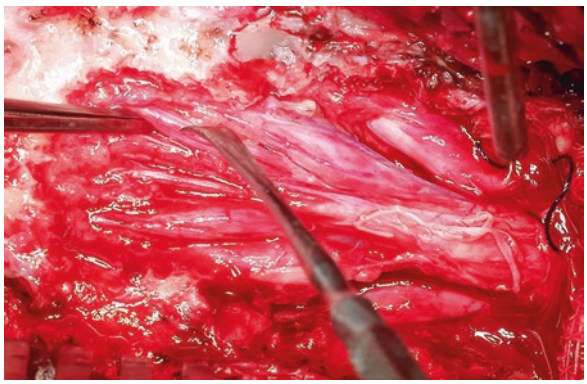

Fig. 36.2 Exposure of sacral roots after extradural laminectomy

Fig. 36.3 Extradural rizothomy. The sensory fibers can be observed attached to the dorsal ganglia and separated from the motor before the rhizotomy

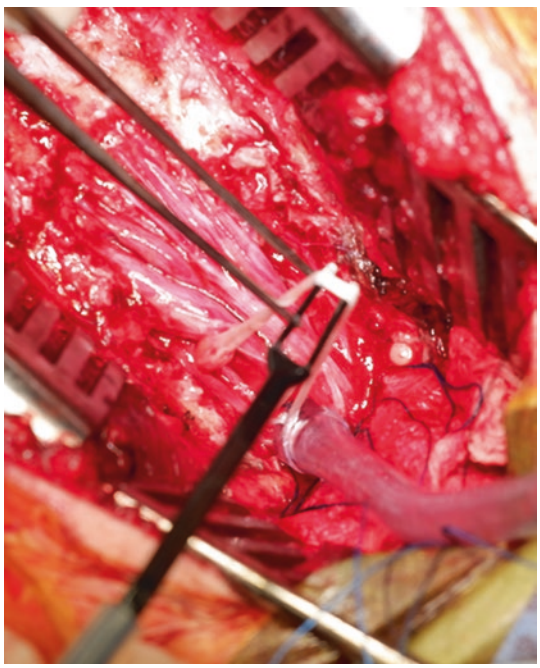

Fig. 36.4 Intraoperative electrical stimulation for root identification: during the stimulation, the autonomic, vesical and motor responses are monitored

Table 36.1 Comparison of the cons and pros between the two techniques [12]

	Pros	Cons
Extradural	Less time consuming Easier approach for urologist No fistula risk Faster recovering	Greater difficulty for sensitive from motor roots Risk of motor damage
Intradural	Roots easier to separate Less risk of motor damage If fails, extradural option is available	Time-consuming process Risk of fistula Arachnoidytis

36.5 Results

Since this surgical technique includes rhizotomies of the dorsal roots S2–S4 (SDAF) plus the implantation of an electric neurostimulator for the ventral roots S2–S4, both storage and voiding disorders are treated with one single procedure: the first part of the operation produces sensory deafferentation by interruption of the sacral reflex arch which suppresses bladder hyperreflexia and detrusor-sphincter dyssynergia thus achieving low bladder pressure and also decreasing autonomic dysreflexia [13]. With the second part of the surgery (SARS), patients regain physiological urination, mediated by a stimulated bladder contraction, thereby eliminating urethral catheterization, the use of anticholinergics and prophylactic antibiotics. With long term follow-up a decrease of the number of urinary tract infections and associated complications has been observed, reducing the number of hospitalizations and the costs associated with these conditions [14]. This outcome has a great positive impact on the quality of life of the patients operated [15].

During the last 40 years more than 2000 patients were implanted [16]. Many groups have since reported their experiences with the Brindley procedure some of them with a follow-up of up to 12 years. The treatment was found to be able to achieve a continence rate of 57–100%, increase bladder capacity by 122–375%, reduction of residual urine volume to <50 mL in 70–91% of patients, and decrease the incidence of UTI [12, 17–19].

Detrusor compliance and storage detrusor pressure have been reported to be improved with SDAF/SARS [18, 20]. Krebs et al. compared pre- and post-SDAF/SARS urodynamic parameters, and found that detrusor compliance and storage detrusor pressure values at short-term follow-up after surgery were greater than 20 cm H_2O/mL and smaller than 40 cm H_2O, respectively. This indicates a return to physiological values. Furthermore, they found an increasing and decreasing tendency in detrusor compliance and storage detrusor pressure, respectively, during the long-term follow-up period [21]. This indicates that further improvement of the urodynamic parameters seems to continue after SDAF.

The stimulation of the anterior root especially of S2 may facilitate erection and the stimulation can maintain the erections, which otherwise would be of short duration. Vignes et al. [22] informs that although the device is effective for erections in 60% of patients, it is only used for this purpose by the 30% of them. As for the bowel function, its utility is better evidenced in the initial period. However, in the longer term the stimulation in their experience is seldom used. Castaño et al. reported that 88% of patients use the device to assist in bowel function, while other authors indicate that the stimulator is used in up to 91% of patients for bowel evacuation [9].

In a cross-sectional study in which 93 patients with the Brindley stimulator were compared with a matched control group of 70 patients, the implanted patient group had a significantly better Specific Impact of Urinary Problems score, a better general quality-of-life index (Qualiveen), a better continence rate, and fewer UTIs, even for those patients who for some reason no longer used the neurostimulator. These patients continued to have the benefits of the rhizotomies as the quality of life and clinical parameters were better [15].

With regard to complications, Brindley et al. [4] reviewed the outcome of 50 patients, and reported seven cases of pain over the sacral dermatomes during micturition with the stimulator. In two patients, the pain was severe and they abandoned the use of the device. The potential risk of pain also underlies the principle that the procedure should be performed only in patients with complete SCI or in some well selected incomplete SCI patients.

The damage of the motor roots is one of the most serious complications since it puts at risk the effect of stimulation. Brindley reported any grade of anterior root damage in 23 of 50 patients [4], although most recovered by 1 year. Cerebrospinal fluid leaks also occurred in 14 patients. To minimize cerebrospinal fluid leaks, Brindley and Sauerwein [23] also attempted extradural implantation, especially in patients with previous arachnoiditis, which may pose significant technical difficulties for intrathecal procedures. The trade-off is an increased risk of anterior nerve root damage. More recently, a study comprising 104 patients who had undergone extradural implantation reported significant improvement in bladder capacity, urinary incontinence episodes and UTIs without any increase in the incidence of anterior root damage [12].

36.6 Conclusion

Sacral deafferentation (SDAF) in combination with a sacral anterior root stimulation (SARS) implant procedure is a valuable treatment option for refractory neurogenic lower urinary tract dysfunction in well selected patients after SCI, and when conservative and minimally invasive treatments have failed. The implantation of the anterior root stimulator offers the ability of voluntary bladder evacuation without the need of intermittent catheterization, preventing catheter associated complications. Quality of life and urodynamic parameters such as detrusor compliance, bladder capacity, and urinary continence are improved whereas detrusor pressure and urinary tract infections are reduced with SDAF/SARS.

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Sacral Neuromodulation

37

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Sacral neuromodulation (SNM) is different than sacral neurostimulation. Neurostimulation describes a technique that stimulates an isolated intact motor neuron system to drive the function it was intended for, e.g. electrical stimulation of the anterior sacral roots to evoke bladder contractions. Neuromodulation on the other hand, is any action that changes or modulates pre-existing neural activity to influence the physiological behavior of an organ.

SNM was first described by Tanagho and Schmidt for treating non-neurogenic bladder dysfunction [1]. In their attempt to use high-frequency anterior root stimulation to fatigue the sphincter, they noted that stimulating sacral roots suppressed neurogenic detrusor overactivity [2]. To perform SNM electrical stimulation is delivered through a lead placed in the third or fourth sacral foramen. SNM is usually performed in two stages. During the first stage, the stimulation lead is connected to an external pulse generation. Two types of leads can be used: a temporary one (a coiled wire with stimulation at the tip) and the definitive lead (with four separate stimulation electrodes). The duration of testing ranges from 5 days up to 6 weeks, depending on the individual implanter and the patient population. A concern for longer test durations is the risk of infection. However after a mean of 52 days no infection or wound-healing disorder was found in a study with a mean follow-up of 33.9 months [3]. After a successful test, the pulse generator is implanted during the second stage. In the majority of studies, success of SNM is usually defined as at least 50% improvement in "relevant" parameters. In case of overactive bladder, these are number of voids (frequency), number of urgency and incontinence episodes, whereas for urinary retention voided volume, number of catheterizations and catheterized volume are considered relevant parameters. It is important to note that detrusor pressure during filling, one of the most important parameters in management of patients with NLUTD, is usually not assessed in the evaluation of success of SNM treatment.

The exact mechanism of SNM is not fully understood. A generally accepted theory is that SNM works through an effect on afferent sensory fibers in the S3 root which modulates voiding and continence reflex pathways in the central nervous system, leading to changes in relevant brain centers [4].

SNM is mostly used in non-neurogenic patients and therefore there is only limited data available on the use of SNM in patient with neurogenic impairment. Furthermore these patients form a heterogeneous group with a wide spectrum of disease processes that change bladder and bowel function depending on the location of the neurogenic lesion. It is therefore not surprising that results may vary between the different neurogenic dysfunctions. In 2010, a meta-analysis on SNM in patients with neurogenic lower urinary tract dysfunction (NLUTD) was published [5]. It included data from 26 trials with mean follow up of 26 months. Success was defined as more than 50% improvement in leakages, pad use, number of voids and number of catheterizations. Only six of the included studies were prospective and the sample size in half of all included studies was less than ten patients. The analysis described pooled success rates during the test phase of 68% in 256 patients and 92% for definitive implant after mean follow up of 26 months [5]. It is important to note that the reported follow up results are per protocol analysis and not intention to treat. Peters et al. reported outcomes for 340 patients of which 71 had NLUTD. Stroke, multiple sclerosis (MS) and Parkinson disease represented the most common causes. A successful test was reported in 63/71 (89%), that subsequently underwent permanent implantation. Sustained improvement was shown for frequency and urgency up to 24 months, whereas

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incontinence was improved during the first 12 months, but was not sustained up to 24 months. Subjective data from a questionnaire showed mixed results in the neurogenic group [6]. Chaabane et al. reported on a group of 62 patients with neurogenic detrusor overactivity (34 patients) and urinary retention (28 patients) due to variety of neurologic diseases. A successful test phase was noted in 61% of the patients. Of the implanted patients 76% reported persistent improvement after 4 years. Patients with peripheral neuropathy responded better than those with Parkinson disease, whereas half of the patients with loss of efficacy had MS [7].

Only limited data are available for the individual neurogenic dysfunctions. A prospective study on 17 MS patients showed in 16 (94%) more than 70% improvement in voiding or storage symptoms. At baseline, all patients had incomplete emptying or were on intermittent catheterization; in 15 patients (88%) detrusor overactivity was demonstrated on urodynamics and in seven patients (41%) detrusor sphincter dyssynergia. All 16 patients with a successful test were implanted. At 3 years follow up 14 (88%) still had their implant successfully working with significant reduction in post void residual volume, reduction in frequency and incontinence episodes. Subjective assessment showed a high degree of satisfaction [8]. In another study in 14 MS patients with urinary retention, 86% success rate has been reported for restoring voiding with a mean follow up of 9 months. Success in reducing incontinence episodes has been reported in 4/5 patients [9]. Before proceeding to SNM in patients with MS it important to discuss the need for future MRI with the patient and the treating neurologist, as currently the device is MRI incompatible (except for 1.5T MRI of the head with head coil). MRI compatible devices are in progress, as are rechargeable pulse generators [10]. Furthermore, disease progression may reduce the efficacy over time.

SNM doesn't seem to have a beneficial effect in complete or nearly complete spinal cord inured (SCI) patients [11, 12]. The only exception is when bilateral stimulation is delivered in the acute phase after SCI. In four patients with complete SCI patients bilateral sacral neuromodulation prevented the neurogenic detrusor overactivity to develop with a mean FU of 26 months [13]. Since only four patients were studied, these results need to be reproduced in a larger study, but if confirmed bilateral SNM in the acute phase after SCI may represent a new minimally invasive technique to prevent deterioration of the LUT. In patients with incomplete lesions beneficial effects of SNM have been reported with success rates varying between 29 and 40% in the test phase and 58 and 80% after definitive implant [5]. Similarly, SNM also improves faecal incontinence in these patients with success rate ranging from 59 to 92% [14].

Although SNM is a minimally invasive technique, adverse events are not that infrequent but are usually easily managed. Loss of efficacy and unwanted stimulation sensation are usually managed by reprogramming. Other adverse events such as lead migration, infection and revision of the pulse generated are reported up to 24% [5], and may require revision surgery. In patients with spinal cord injury lead migration may occur more often than in non-neurogenic patients. In patients with diabetes, explanation rates due to infection up have been reported up to 17% compared to 4% in non-diabetic patients [15].

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Pudendal Neuromodulation

38

Michele Spinelli, Giulio del Popolo, Julien Renard, and Stefan De Wachter

38.1 Electrical Modulation of the Pudendal Nerve

As the pudendal nerve is one of the major nerves which stimulates the pelvic floor muscles, the external urethral and anal sphincters and the pelvic organs, this nerve is being increasingly investigated as a treatment option, particularly patients with neurogenic OAB.

The pudendal nerve is composed of nerve fibers originating from S2 to S4 nerve roots which innervate the pelvic floor muscles, the external urethral and anal sphincters, and the pelvic organs. It is a mixed nerve that contains somatic and autonomic nerve fibers.

The pudendal nerve leaves the pelvis via the intra-piriform foramen and passes dorsally in an arc around the ischial spine through the lesser sciatic foramen into the ischio-rectal fossa and before leaving the Alcock's canal (pudendal canal) divides into two terminal branches: the perineal nerves and the inferior rectal nerves.

These nerves supply motor and sensory innervations to the striated muscles (bulbocavernosus muscle and external anal sphincter) and partly to the urethra and the dorsal nerve of the penis or clitoris. The caudal portion of the pudendal nerve runs through the pudendal canal, which lies against the sidewall of the pelvis and duplicates the fascia of the obturator internus muscle.

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Anatomy, physiology and neurophysiology of the pudendal nerve have been studied extensively, particularly when its role in continence mechanisms has been more elucidated [1, 2]. One of the first works investigating the clinical significance of pudendal nerve anatomy was performed by Juenemann et al. [3]. However, already in 1986 Vodusek et al. described detrusor inhibition induced by stimulation of pudendal nerve afferents in ten patients with suprasacral spinal cord lesions and detrusor hyperreflexia [4]. The authors demonstrated that in patients with neurogenic lower urinary tract dysfunction, electro stimulation of the sacral root and pudendal nerve markedly increased intra urethral closure pressures.

Today, there is much knowledge obtained on the pudendal nerve anatomy and innervations' role. New studies continue to be performed to further assist physicians operating in close proximity to this nerve or when using this nerve for various therapeutic applications. These studies should also help to get a better understanding of the underlying neuronal mechanism and the involved pathways in humans when the pudendal nerve is stimulated.

Due to the anatomy of Alcock's canal, surgical exposure of the nerve has been difficult in the past due to the increased risk of damage to the nerve itself, but with recent developments in the implant procedure and equipment, chronic Pudendal Nerve Stimulation (PNS) can now be easily achieved. Anatomy of the pudendal nerve and its terminal branches from a cadaver was published by Schraffordt et al. in 2004 [5]. This study documented the anatomy of the pudendal nerve by looking into 28 cadavers, in order to examine the course of the pudendal nerve and its branches in the perineum. The study concluded that a sound knowledge of the anatomical variations of the pudendal nerve and its branches is essential for all surgeons operating in the perineal region.

Today, chronic pudendal nerve stimulation can easily be performed using the existing InterStim device. The treatment is minimally invasive by using a percutaneous approach to reach Alcock's canal [6]. A permanent tined lead can be implanted in the first implant stage to evaluate the clinical efficacy; this avoids any risk of efficacy changes when the

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_38

permanent INS is implanted. The tined lead, which was originally developed for sacral nerve stimulation, to create a more secure lead position has also contributed to making pudendal nerve stimulation a safe option for surgeons and patients [7]. Additionally, neurophysiological monitoring helps to implant the lead in the correct position, and helps to verify effective stimulation.

This monitoring is done by assessing electromyographic activity (EMG) of the external anal sphincter (EAS). A cadaver study, published by Reitz in 2007 [8], provides data which indicates safe needle placement via the posterior approach, which is the approach used by author.

38.2 Surgical Technique

38.2.1 Lead Implant

The patient is placed in prone position. Bony topography is drawn with the use of a fluoroscopy X-ray device in order to spot the greater trochanter and the ischial tuberosity (Fig. 38.1). These two reference marks are used to find the two points as schematic images shows below (Fig. 38.2).

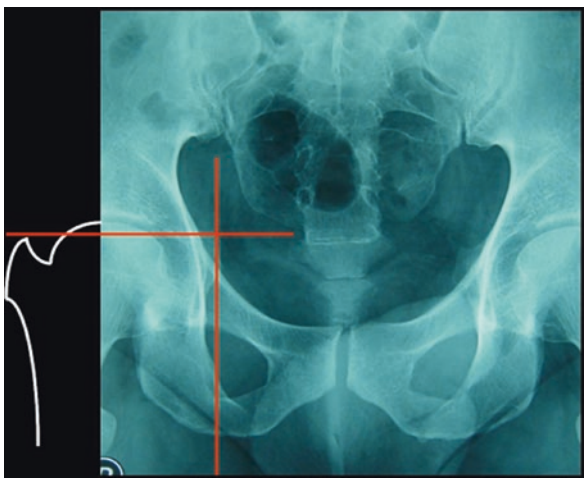

Fig. 38.1 X-ray showing lead insertion position

This technique is recommended to stay clear of veins and arteries and to avoid possible needle punctures or injections of anesthesia directly into the vascular system. The X-ray C-arm should be ready to perform anterior-posterior image of the pelvis. Locate the ischial tuberosity tip (ITT) and the greater trochanter (GT) with a pair of 90° angle crossed stylets placed on the patient's skin, mark with a dot where the stylets cross.

Puncture the intersection of the lines drawn vertically from the ITT and horizontally from the GT, as demonstrated in Fig. 38.2.

38.2.2 Preparation for Lead Insertion

Anesthesia should be administered to the patient only if proceeding with lead implant after skin drawing. Muscle relaxants should not be used. Avoid general anesthesia. Anesthetic choices include Lidocaine solution for injections, maximum dose is 500 mg for healthy patients; Bupivacaine with maximum recommended dose of 200 mg. Dosage should be minimized to preserve nerve response. Minimize the risk of vascular absorption by injecting slowly and in small boluses local anesthetic or chemotoxic substances, aspirate before injecting.

38.2.3 Acute Test with Test Needle to Locate Optimal Position

Place patient in a prone position, prepare the patient's lower quadrant and connection site, and prepare perineum, gluteus and sacrum for sterile surgery. Drape to allow observation of the pelvic floor for muscle response to test stimulation. Clean dry skin area, and affix the ground pad to it. Electromyography recording needle is gently inserted in the anal sphincter stimulation. Patient stimulation cable is connected to electromyography output. Vertically insert the insulated foramen test needle. Connect the mini-hook from the patient cable to the non-insulated part of the foramen needle and stimulate, see Fig. 38.3.

Fig. 38.2 Diagrammatic view of lead puncture insertion position

A 1 mA step increasing pulse current from 0 is used to locate the tip of the needle adjacent to the pudendal nerve by comparing the generated CMAP with the reference trace. An acceptable CMAP should be within a variability of 2 ms compared with the reference trace.

When satisfied with the needle position, replace needle stylet with the directional guide. Holding the directional guide remove the foramen needle. Make a small incision on either side of the directional guide. Fit the dilator and introducer sheath over the directional guide and advance to the third most proximal depth marker on the directional guide with the top of the dilator, see Fig. 38.4.

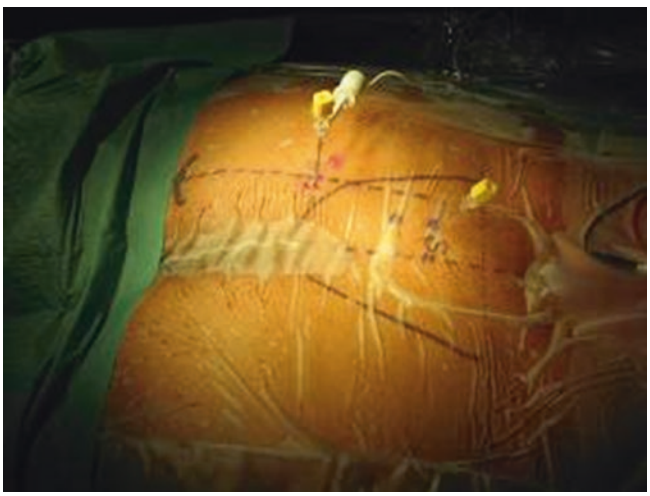

Fig. 38.3 Acute test with test needle

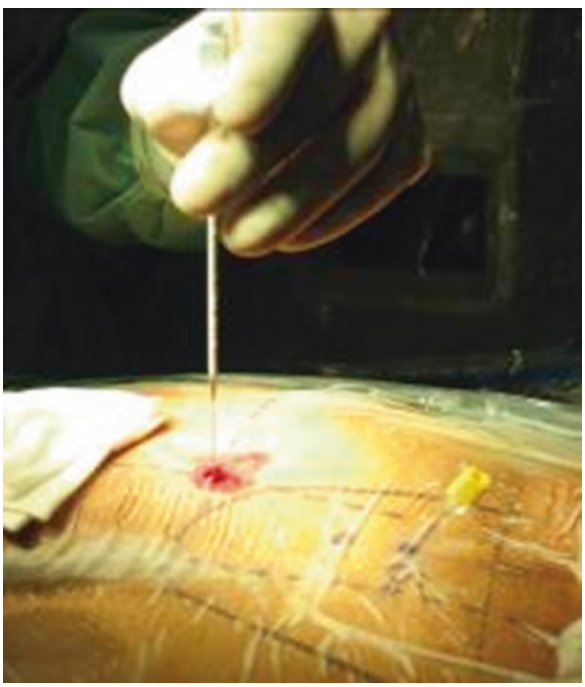

Fig. 38.4 Preparation for tined lead insertion

38.2.4 Tined Lead Insertion

While holding the lead in place, retract the introducer sheath until the second visual marker lines up with the top of the introducer sheath handle. A 1 mA step increasing pulse current from 0 is used to locate the tip of the needle adjacent to the pudendal nerve by comparing the generated CMAP with the reference trace (Fig. 38.5). Stimulate the various electrodes and observe the generated CMAP, see Fig. 38.6.

Hold sheath and lead together when adjusting lead position.

When satisfied with the lead position, hold the lead in place and carefully withdraw the introducer sheath and the lead stylet. Ensure the lead is in the correct position before deploying the tines. Do not dislodge the lead as tines are deployed. Stimulate the four electrodes to confirm the CMAP previously observed. If you need to advance lead after tines are deployed do so after lead stylet is inserted. If you need to retract do so completely using gentle traction and place it again.

38.2.5 Tunnelization from Pocket Site to Incision Site and Lead Connection to the Test Stimulator

Identify the site for the neurostimulator subcutaneous pocket. Make a small opening large enough for the percutaneous extension-lead connector at the future neurostimulator pocket site. Either abdomen or buttocks are suitable sites. Make a tunnel from the pocket site to the incision site. Lead tunneling should not be too deep. Gently feed the lead through the tube, remove the tube and keep the lead in place, close the lead implant incision, and dress the wound appropriately. Make a small incision contro-lateral to the neurostimulator pocket site where the percutaneous extension

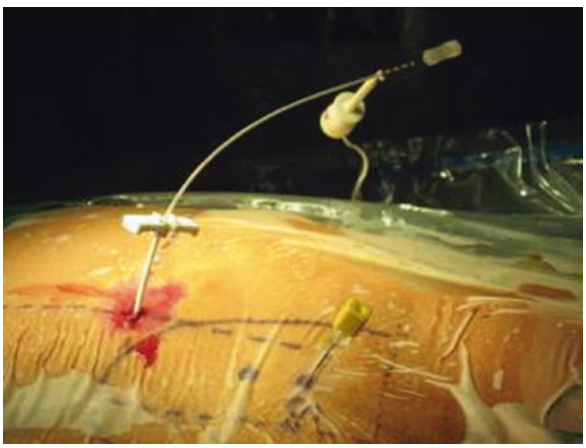

Fig. 38.5 Tined lead insertion

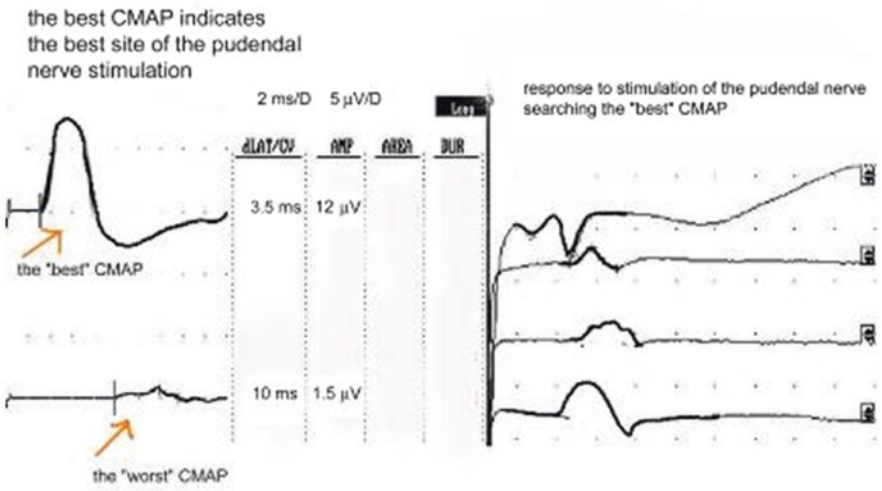

Fig. 38.6 Review of CMAP to locate best tined lead position

will exit the skin, tunnel at the subcutaneous level from the pocket to the stab wound. Connect the lead and the percutaneous extension, position the lead and extension in order to avoid sharp bends or kinks. Insert lead into percutaneous extension screw set connector. The connection to the test stimulator is now available for test stimulation. Tunnel the lead to the future neurostimulator pocket site. Close the initial incision and staple the wound leaving only the fine percutaneous extension wires and pin connector protruding from the skin.

38.2.6 Parameter Settings

Suggested parameter settings in the test stimulator are: bipolar stimulation between the best stimulating electrodes, frequency of 5 Hz, pulse width 210 ms, continuous mode, amplitude as low as possible (1–5 V below patient's sensitivity). It is not suggested to seek for patient sensory responses.

The patient should be carefully instructed about hygienic and general conduct during the test phase. In addition to providing the patient manual, explain the procedure for managing the test stimulator.

If any adverse events occur during the first stage implant, these will be recorded and documented.

38.3 Review of Experience

We present here the results of our clinical experience with pudendal neuromodulation which helped us in defining always more precisely the correct indications and the future directions to take.

This is a retrospective analysis of all patients undergoing pudendal neuromodulation at the Alberto Zanollo Center in Milan. We registered type of disorder (complete or partial spine lesion, medullary ischemia, myelitis, idiopathic, iatrogenic) and the corresponding functional disorder. Endpoints were control of storage and voiding symptoms. All patients were evaluated through pre and post operative up bladder diaries, urodynamics, need for catheterization. Procedure was performed as described in the previous chapters. All data was collected prospectively. Endpoints of this analysis were

- Improvement of storage and/or voiding symptoms
- Reduction of urgency and/or frequency at bladder diary
- Reduction of leakage

Response was defined as reduction of leakage or interruption of autologous catheterization.

In terms of results since May 2003, 64 patients received pudendal neuromodulation for both storage symptoms (neurogenic or undisclosed neurogenic detrusor overactivity) and voiding insufficiency (urinary retention over detrusor sphincter dyssinaergia). Concerning the neurological disorders, 6 patients were complete spinal cord lesion (ASIA A); 16 were incomplete lesions (ASIA B or more); 9 infectious cases (myelitis); 2 tethered cord; 1 Arnold Chiari malformation. Three patients formed the iatrogenic patients group, suffering from overactive bladder following radical prostatectomy, post hysterectomy and one patient presenting voiding insufficiency after endometriosis resection. The remainder of the cohort suffered from idiopathic (undisclosed neurogenic) overactive bladder refractory to sacral neuromodulation.

Mean follow up was 94 ± 44 month. Overall the non-responder rate was 50%. It included all complete cord lesions (ASIA A) patients, 38% of incomplete lesion, 22% of myelitis and 14% of idiopathics. One of the two patients with tethered cord responded to treatment. The patient affected with an Arnold Chiari malformation did not show improvement

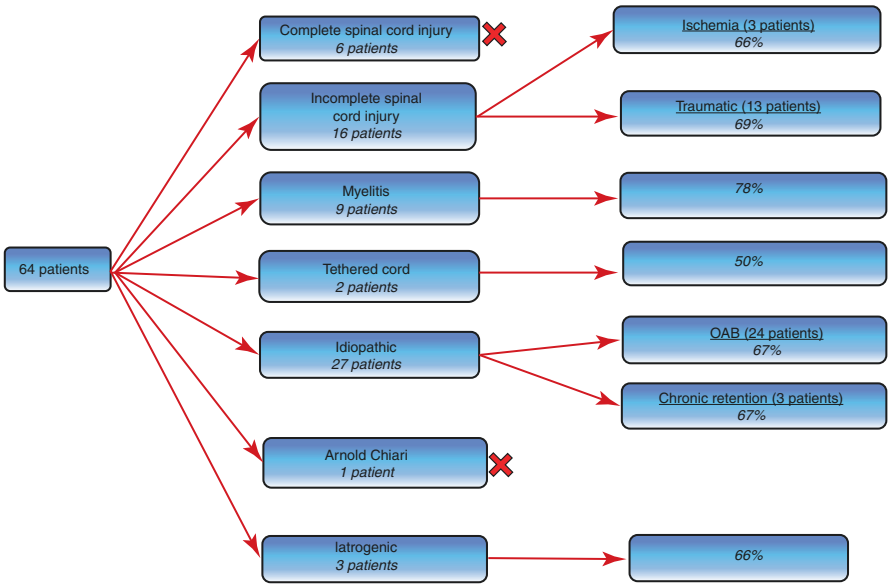

Fig. 38.7 The results of 64 patients received pudendal neuromodulation

after treatment. The results are summarized in the following diagram (Fig. 38.7).

For responders, all showed an improvement of urgency but not voiding insufficiency. Only 10% of patients affected with both voiding and storage symptoms showed improvement of both problematics. Patients implanted for sole urinary retention responded in 2/3 of cases.

Non responders underwent botulinum toxin indetrusorial injections while all voiding insufficiency was managed by self catheterization.

It is important to point out that not all patients underwent post operative urodynamic evaluation reason why these data are not presented here.

In conclusion this review of experience helps showing that there is space for pudendal nerve stimulation in management of pelvic floor disorders. Response, although with medium rates, can be obtained in "classic" neurogenic bladder or in non responders to sacral neuromodulation. It therefore opens the way to further research protocols, which could include bilateral or mixed stimulation or evaluate new settings of stimulation. It is clear that this will be linked to developments of new leads and generators always thriving to restore a balance of the nervous system.

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Implantable Chronic Tibial Nerve Modulation (CTNM)

39

Karl-Dietrich Sievert

39.1 The History from Acupuncture to CTNM

Peripheral neuromodulation is derived from techniques used in traditional Chinese medicine, better known as acupuncture. The earliest writings about "stone needles" (called Pien in Chinese) date from about 500 BC. Puncturing specific points was believed to restore "the energetic harmony" of the body [1]. In 1683, Willem ten Rhijine discovered this Eastern traditional way of medicine and published a book entitled Dissertatio de Arthritide: Mantissa Schematica: De Acupunctura: Et Orationes tres [2]. He was the first Western physician to describe the technique he called "acupunctura," where needles were used to treat a variety of diseases. One of the most common acupuncture points is the San-Yin-Jiao point or Spleen 6 (SP-6) located on the medial side of the lower leg, about 4 finger breadths cephalad to the medial malleolus. The location of SP-6 and the organs affected by its stimulation have remarkable similarities with current posterior tibia nerve stimulation (PTNS). In combination with the applied ground patch, an electrical current is applied to the acupuncture needle, which transforms into an electrical form of acupuncture.

McGuire et al. were the first to report the use of PTNS in 22 patients with neurogenic OAB. PTNS was effective in 87% of the patients who demonstrated a complete or partial improvement of their symptoms [3]. They described the effect of PTNS as a inhibition of detrusor activity and as a result improving voiding symptoms [3]. Subsequently, Stoller et al. further developed PTNS (known as Stoller afferent nerve stimulation (SANS)), as a clinical treatment for OAB, with promising results applying electrical stimulation through an electrode located near the medial malleolus [4, 5].

Subsequent clinical trials led to PTNS FDA approval (the Urgent® PC Neuromodulation System, Cogentix Medical Inc., MN, USA) in 2005 for the treatment of urinary urgency/frequency and urge incontinence. This device received the CE mark within the same year for similar indications and even fecal incontinence. More recently, Medtronic Inc. developed the NURO™ system and received approval for marketing but they all remained as acute treatment options.

39.2 Neuro-anatomy and Neurophysiology of the Lower Urinary Tract (LUT)

Stimulation of the hypogastric plexus (spinal level T10-L2) results in sympathetic relaxation of the detrusor muscle and contraction of the intrinsic sphincter thereby facilitating the storage phase of the bladder cycle and suppressing the desire to void. Stimulation of the parasympathetic nerves, via the sacral micturition center (spinal level S2-S4) travels to the pelvic nerve resulting in the contraction of the detrusor muscle (via release of predominantly cholinergic transmitter) and relaxation of the sphincter that facilitates voluntary micturition. Somatic nerves from S2 to S4 innervate the pelvic floor and external urethral sphincter via the pudendal nerve with 70% of external urethral sphincter pressure dependent upon efferent activity from S3 ventral root, and S2 (and possibly S4) contributing the remaining 30% [6]. Afferent pathways provide a sense of bladder fullness and allow initiation of micturition. There are two types of bladder afferent pathways that travel via the pelvic nerve to the sacral micturition center (S2-S4); A-d fibers from mechanoreceptors in the bladder wall detecting fullness and C-fibers carrying noxious or painful signals e.g. during a urinary tract infection. The smooth coordination between the two bladder states of storage and micturition depend on intact neural pathways in the central nervous system (cortical and pontine micturition centres) that provide amplification, coordination and timing.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_39

The bladder is an unusual autonomic visceral organ in that once toilet training is achieved, voluntary initiation of voiding over a wide range of bladder volumes can be initiated at will in an "on-off" manner that is facilitated via a series of positive feedback loops using supra-spinal pathways. The initial concept that babies void via a reflex spinal pathway is no longer held with evidence that neonates are aware of the involvement of CNS centers and later development of voluntary control [7–9].

39.3 Percutaneous Tibial Nerve Stimulation (PTNS)

Percutaneous tibial nerve stimulation (PTNS) has been shown to be effective in managing storage symptoms and improving urodynamic parameters in patients with multiple sclerosis (MS) [10–12]. Initial PTNS is commonly performed as an office procedure in weekly 20–30 min sessions over a period of 10–12 weeks, and generally followed by a period of maintenance therapy, of which the optimal characteristics are poorly defined. This therapy is safe, the patients' reported subjective and objective cure rates of 60–80%. Their treatment satisfaction is generally high (70%) and their overall quality of life is usually improved substantially [10, 12–15]. Data from a study of 19 MS patients who received weekly, 30 min PTNS for 12 weeks revealed a significant improvement in urodynamic parameters, including maximum cystomanometric capacity (increased from 199.7 to 266.8 mL; $P < 0.001$), maximum detrusor pressure at maximum cystomanometric capacity (decrease from 48.8 to 35.8 cm H_2O; $P = 0.001$), maximum flow rate (increased from 11.6 to 13.2 mL; $P = 0.003$) and post-void residual volume (decreased from 82.9 to 48 mL; $P = 0.006$) [16].

The efficacy of PTNS has been proven in a multi-center study of a cohort of 70 MS patients and symptoms of overactive bladder (OAB) [17]. All patients received PTNS for 20 min per day for a period of 3 months. Clinical improvement in symptoms was observed in 82.6% and 83.3% of the patients on day 30 and day 90, respectively, with significant improvements in urinary urgency, frequency, patients' self-reported symptoms, continence and quality of life observed between day 0 and day 90 of the study ($P < 0.05$ for all changes) [17]. The initial acute response (defined as a >30% increase in bladder capacity and/or reflex volume) to the first session of transcutaneous stimulation was positive in 51.2% of patients, without any notable correlations with longer-term clinical effectiveness of the treatments [17].

The effectiveness is discussed through different pathways, which are recently discussed:

- Mast cell count in the bladder diminished [18]
- Effect on the spinal cord by reducing C-fos expression [19]
- Possible reorganization of cortical excitability [20]
- In the central nervous system by inhibiting the ascending or descending pathways of the spinobulbospinal micturition reflex [21]
- Age-related changes in skin function may affect brainstem functions regulating visceral activities [22]

As a result of the possible effectiveness in the group of neurogenic patients in the initial publications with chronic implants in idiopathic patients, it would be logical to evaluate the efficacy in neurogenic patients as well. Based on fecal incontinence in MS patients in non-randomized studies, SNM and PTNS seems to be comparable in efficacy [23]. Although PTNS appears to be more cost effective than SNM, it more likely that the patients utilizing PTNS will discontinue therapy [24]. There is only very small amount of data available for chronic tibial nerve modulation (CTNM) in nOAB patients despite there being a number of different implants in clinical studies or already available in different markets.

39.4 Introduction of Chronic Tibial Nerve Modulation (CTNM) Implants

39.4.1 Bioness Stimrouter Neuromodulation System

The Bioness device can be implanted under local anesthesia and consists of an implanted lead with an integrated receiver, anchor and three electrode contacts adjacent to the posterior tibial nerve. The wireless lead captures stimulation energy delivered transdermally from an external pulse transmitter and electrode patch (see Fig. 39.1a). The external pulse transmitter is rechargeable and is only worn on the skin surface during periods of stimulation (see Fig. 39.1b). A patient programmer is used to track usage and change programs in the device. The programmer controls the external pulse transmitter with wireless radio frequency. This device has previously been tested in patients with chronic pain demonstrating no device-related serious adverse event (SAEs) [25]. In a prospective, multicenter, randomized, double-blinded trial, 94 participants were enrolled to assess the safety and efficacy of CTNM for patients with OAB symptoms [25]. The treatment protocol instructs patients to apply stimulation for at least 3 days and up to 7 days per week, for at least 30 min per day for a total of 6 months. The results of this study have been only reported for the 3 months results [26].

39.4.2 BlueWind Medical Miniature Implant

The implant called RENOVA is battery-less, wirelessly powered and delivers stimulation to the tibial nerve (see Fig. 39.2a). The technology is currently only available in

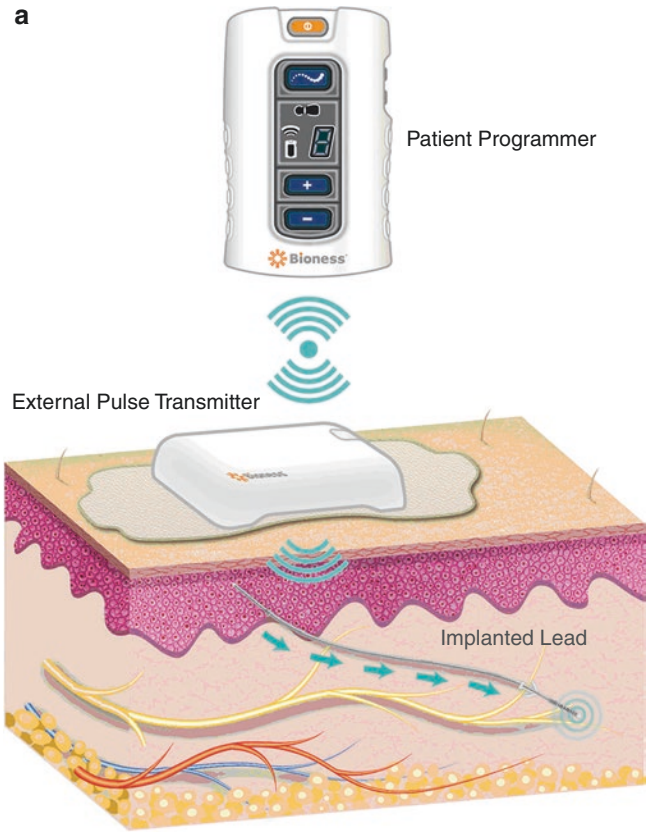

Fig. 39.1 (**a**) Bioness Stimrouter neuromodulation system [32]. (**b**) Transmitter worn on the skin's surface [32]

one model, which is surgically implanted through a small incision and fixed by a stitch close to the tibial neurovascular bundle, which can be performed under local or general anesthesia. For the percutaneous technique, the device (will be soon become available) is inserted using a designated delivery system and positioned under ultrasound or active stimulation guidance (Fig. 39.2b). The wireless device is powered through an external control unit that controls the therapeutic parameters and is worn by the patient as an ankle bracelet during treatment at home (see Fig. 39.2c). A physician sets the individual stimulation parameters in the program. The recommended company treatment protocol is 30 min daily of self-administered treatment while carrying on normal daily activities. A prospective multi-center study assessing the safety and performance of the RENOVA system in the treatment of patients with OAB with or without urgency incontinence was recently concluded. The results of this study were presented at the International Continence Society (ICS) meeting in 2016 where the outcomes of 34 subjects were analyzed and followed up on for up to 6 months. Results showed that 71% of the participants experienced over a 50% improvement in OAB symptoms at the 6-month follow-up, with 27.6% of urgency incontinence subjects being dry at the 6-month follow-up [27]. A single serious adverse event was reported (2.8%) requiring implant removal with no further complications reported by the authors at the 6-month follow-up.

39.4.3 StimGuard Implant 1.5 and 3 Tesslar MRI [28–30]

A passive micro-sized device with integrated anchors (Fig. 39.3a) which was reduced further to the actual length of 6 cm which fits through a 14–16 GA needle. Although it is currently only used in trials, the longer model has received CE and FDA approval for SNM. The implant is approved for MRI (1.5 and 3 Tesslar) which is regulated and powered through the external rechargeable device.

The external pulse transmitter is rechargeable and only worn during periods of stimulation (see Fig. 39.3b). A patient

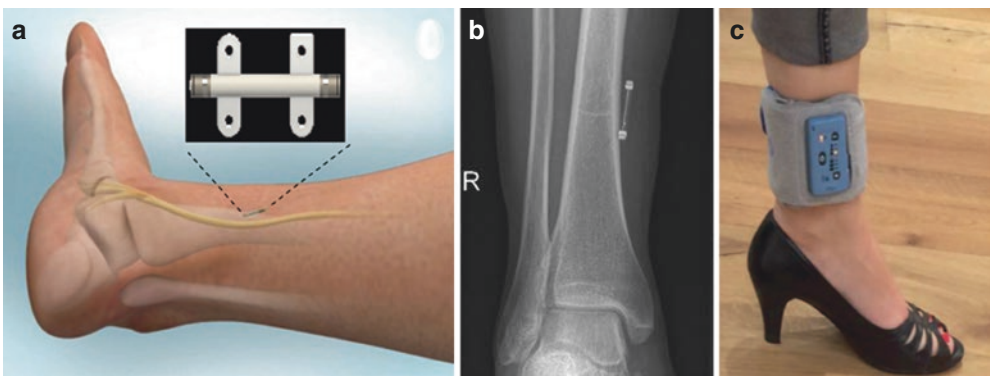

Fig. 39.2 (**a**) BlueWind Medical miniature implant [33]. (**b**) X-ray of implant in the leg [33]. (**c**) Transmitter worn on the leg [33]

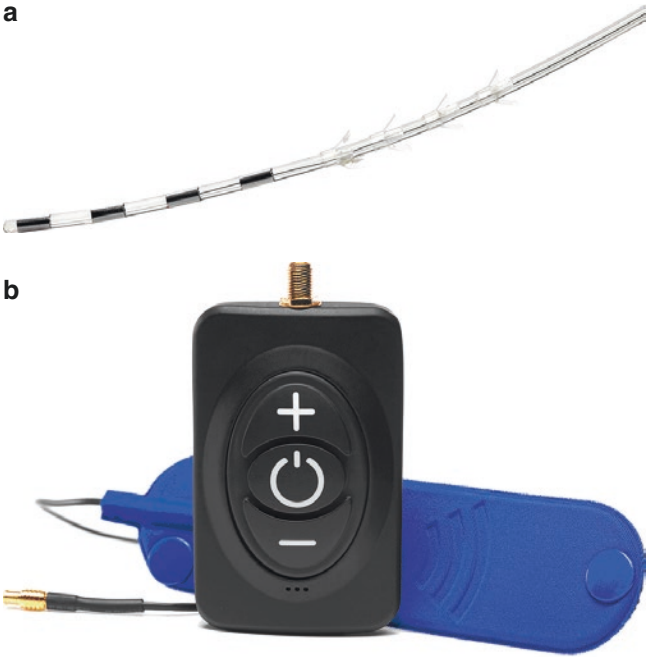

Fig. 39.3 (**a**) Current StimGuard implant (picture provided by StimGuard®). (**b**) The external device (black) with the locally placed antenna (blue) (picture provided by StimGuard®)

programmer is used to track usage and change programs in the device. The programmer controls the external pulse transmitter with wireless radio frequency and provides the opportunity to perform software updates which will minimize the need for implant exchanges. The external unit can be easily worn under clothing. Stimulation is suggested during the sleep period.

The limited data available for neurogenic patients has been reported at the annual International Continence Society meeting in 2015 [31]. In an initial setting two neurogenic male received bilateral StimWave® implants: an 82 year old man with Parkinson's disease for the last 6 years and a 69 year old male with Multiple Sclerosis (MS) for the last 16 years. Both patients suffered from overactive bladder. Under local anesthesia, the patients received their implants which was verified by fluorescent and intraoperative stimulation (movement of the big toe). Within 2 weeks both patients reported significant improvement related to the primary complaints of urgency and nocturia. In the Parkinson's patient, functional bladder capacity increased significantly (370–510 mL) and voided volume increased (370–480 mL) without an increase of the post void residual (0–30 mL). The initially detrusor overactivity was resolved 2 month post-operatively. Although the Parkinson's patient reported ongoing improvement, he stopped the treatment because he was concerned that the CTNM was the primary cause for the progression of his Parkinson's disease.

In the MS patient bladder capacity doubled (100–200 mL) and urge incontinence dropped from four times to once a day, however, the implant migrated though the skin after 2 years. The implant was easily removed without sign of infection simply by pulling it out (the initial implant did not have an anchoring system) and was fixed subcutaneously by a silk suture.

In addition to these initial neurogenic patients, several idiopathic patients have already received chronic implants for iOAB, however, an official clinical study with CTNM for neurogenic patients is still missing. Meanwhile, the StimWave® implant has under gone further improvements, especially with the tines to hold it in position. There are reports about the successful treatment of neurogenic OAB by PTNS and there is initial evidence that CTNM can significantly improve the OAB in those patients. In addition to stimulation through an external device, the implant is approved for the 1.5 and 3 Tesslar MRI in the leg location. Usually the lower leg is not of interest in the neurological MRI investigations compared to the spine. With the recent received CE mark and FDA approval of the StimWave® SNM Implant, this product provides the opportunity to investigate the complete spine with only a minimal erasement around the implant whereas the other approved products only allow an MRI of the head.

In addition the system provides the patient with the opportunity to perform CTNM during the night (the external rechargeable device lasts for 6–8 h). Therefore the patients performed CTNM while they were sleeping on a subsensory threshold. The device made them independent resulting in a significantly increased QoL; whereas for the PTNS, patients came to the office once a week for a 20 min treatment in addition to the travel time to the office and back as well as waiting time, which decreased their QoL.

In conclusion: The upcoming CTNM improves the individual patient's quality of life and makes them more independent when compared to common PTNS.

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Part XII

Detrusor Myoplasty

Bladder Covering by Striated Muscle

40

Karl-Dietrich Sievert

Abstract

Bladder acontractility caused by a lower motor neuron lesion is an irreversible and debilitating voiding disorder affecting a large number of relatively young people. In the following, based on our pilot study (Gakis et al., J Urol 185:593–9, 2011), we present the clinical long-term results in a multicenter setting concerning the Latissimus Dorsi Detrusor Myoplasty (LDDM) in patients with an acontractile bladder for whom there is no treatment alternative than lifelong clean intermittent catheterization (CIC). From May 2001 to February 2008, 24 patients (mean age: 37 years; range: 14–63; 15 males, 9 females) were enrolled in four clinical centers worldwide requiring complete CIC 4–8 times/day. The mean follow-up was 46 months (8–89) and was carried out by questionnaire and measurement of post-void residual urine volume (PVR). Seventeen of the 24 patients (70.8%) gained complete spontaneous voiding and do not require further CIC with PVR from 0 to 100 mL. In three patients (16.5%), the frequency of CIC was reduced from 4–6 times/day preoperatively to 2–4 times/day postoperatively with RUVs from 150 to 250 mL. Twenty-one of 23 patients (91.3%) have no recurrent urinary tract infections postoperatively (mean preoperatively: 7.8/year; 0–24). At present, four patients (12.5%) need CIC 4–6 times/day as before. No functional restrictions or chronic pain of the operated upper extremity were observed in any patient. Complete (n = 17) or incomplete spontaneous voiding (n = 3) was achieved in 20 of the 24 patients (83.3%). Recurrent urinary tract infections terminated in 21 of the 23 patients postoperatively (91.3%). These results have been maintained during the long-term follow-up period of up to 7.5 years.

40.1 Background

Most patients diagnosed with detrusor acontractility have a history of increasing residual volume (RV) or as described from the patients history that they were able to hold urine longer than the others, which suddenly tipped into retention. Also, bladder acontractility is supposed to be caused by a lower motor neuron lesion as an irreversible disorder [1]. The underlying pathological mechanism of bladder acontractility may be due to the damage to the detrusor muscle itself, its autonomic nerve supply or the spinal micturition center [1].

The primary treatment option is the lifelong clean, intermittent catheterization (CIC) with comorbidities as urethral laceration, recurrent urinary tract infection, occasional bladder perforation and possible renal function deterioration. Especially younger male see the lifelong catheterization as a psychological burden, which is often the reason for further worsening and additional side effects as hydronephroses and kidney failure in the long term as well as the socioeconomic effect [2].

Studies investigating restoration of voluntary bladder emptying by sacral neuromodulation demonstrated these approaches as not effective enough due to a lower motor neuron lesion [1, 3, 4]. If the treatment is started early enough as demonstrated in children, Intravesical Electrical Stimulation (IVES) seems to have a lasting beneficial effect [5].

In a long term study early animal study von Heyden et al. demonstrated: (1) the ability of the transposed latissimus dorsi muscle to evacuate a bladder-like reservoir; and (2) the regenerative potential of muscle and nerve after nerve transection and repair [6]. They were able to evacuate 63.8 ± 6.2% of the reservoir's volume by stimulation of the thoracodorsal

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_40

nerve with a maximum pressure of 109.5 ± 18.6 cm H_2O. Four months later after reanastomosed for transcutaneous stimulation they recorded the pressure generation at regular intervals for 8 months 79.3 ± 12.1 cm H_2O (72.4% of the initial value) and were able to evacuate 48.3 ± 6.7% of total volume.

In the first clinical study Stenzl A et al. reported the successful Latissimus Dorsi Detrusor Myoplasty (LDDM) in three patients who had acontractile bladders related to spinal-cord injury and chronic overdistension for 2–5 years prior to the surgery [7]. On urodynamic assessment at 12 months after the operation bladder capacity was found to be 600 mL, 600 mL, and 650 mL, residual urinary volume 0 mL, 50 mL, 90 mL, and maximum flow rate 26 mL/s, 25 mL/s, and 18 mL/s, respectively [7].

As reported in the first clinical experience the indication is the detrusor acontractility, related to spinal trauma below the Th12, tethered cord syndrome, lumbar hernia of nuclei pulposi, megacystis/bladder outlet obstruction, sacral myelomeningocele, and idiopathic and chronic retention after hysterectomy. Patients with an upper motor neuron lesion should be excluded. In relation to the situation that patients might be doing a certain sport where they might need the latissimus dorsi muscle, the patient should be asked about sport preferences and activities such as golf, tree climbing or others.

Indications for the latissimus dorsi detrusor myoplasty [8]

- Bladder acontractility without upper motor neuron lesion
- No indication for neuromodulation
- Life expectancy greater than 10 years; the patient should be <60 years of age [9]
- No improvement of bladder dysfunction longer than 1 year
- Patient should be able to handle clean intermittent catheterization
- Catheterization greater than 1 year
- No infravesical obstruction
- Intact 12th intercostal motor nerve

In cases of equivocal urodynamic findings, sacral neuromodulation should be applied to rule out the presence of bladder hypocontractility rather than acontractility.

In the routine evaluation of the patient should include:

- Video-urodynamics
- Diagnostic urethrocystoscopy
- Excretory urography
- Electromyography of the lower portion of the rectus abdominis muscle
- Neurophysiologic assessment of the sacral district, including MRI or CT

40.2 Surgical Technique of LDDM

The harvesting and transplantation of the latissimus dorsi muscle is carried out simultaneously by two surgical teams (urologic and plastic surgeons) [6]. After a generous zigzag-shaped incision in the axilla, which enables the essential long dissection of the neurovascular thoracodorsal pedicle, the latissimus dorsi muscle, the main branches of its supplying thoracodorsal vessels and the nerve of the latissimus dorsi muscle have to be completely elevated. The neurovascular bundle is not transsected until the recipient vessels and nerve had been prepared for microanastomosis. The urological team freed, via an extraperitoneal midline abdominal or Pfannenstiel incision, the bladder down to trigone. Subsequently, both ischial bones and insertions of the sacrospinal ligaments become visual, where individual stiches are placed to become the base attachment for the transferred latissimus dorsi muscle.

After identifying the lowest motor branches of the intercostal nerve and the ipsilateral inferior epigastric artery and vein, the transferred latissimus dorsi muscle was microsurgically anastomosed immediately. The latissimus dorsi muscle was attached to the above structures in the pelvis by the preplaced sutures [10–12] (Fig. 40.1).

40.3 Postoperative Care

Initially the bladder was drained by a transurethral catheter and subsequently by CIC for a total of 3 months. Afterwards, under physiotherapeutic guidance, the patients were instructed to void by voluntarily contracting the lower abdominal muscles. Catheterization intervals were gradually increased depending on the residual urinary volumes. In the follow-up the vascularization and function was monitored by Doppler-ultrasound and urodynamic assessment [10, 11].

Although the LDDM has been performed primarily in one center over the last two decades, the numbers of published cases remains low. There have been requests to improve the outcome related to the invasiveness of the surgery in order to find more precise investigation methods/criteria to minimize failure [13]. However, a success rate of over 83% (complete (n = 17) or partial spontaneous voiding (n = 3) was achieved in 20 of the 24 patients) with a follow-up time of up to 7.5 years, which appears satisfactory. In 50% of those patients where the authors reported failure, major postoperative complications were recorded (Clavian III), Table 40.1 [12].

Therefore it might be not be an aspect of the preoperative evaluation which determines the outcome as was suggested during the pre-operative investigation [14]. Eight of 15 male patients (53%) that underwent a LDDM, later underwent a

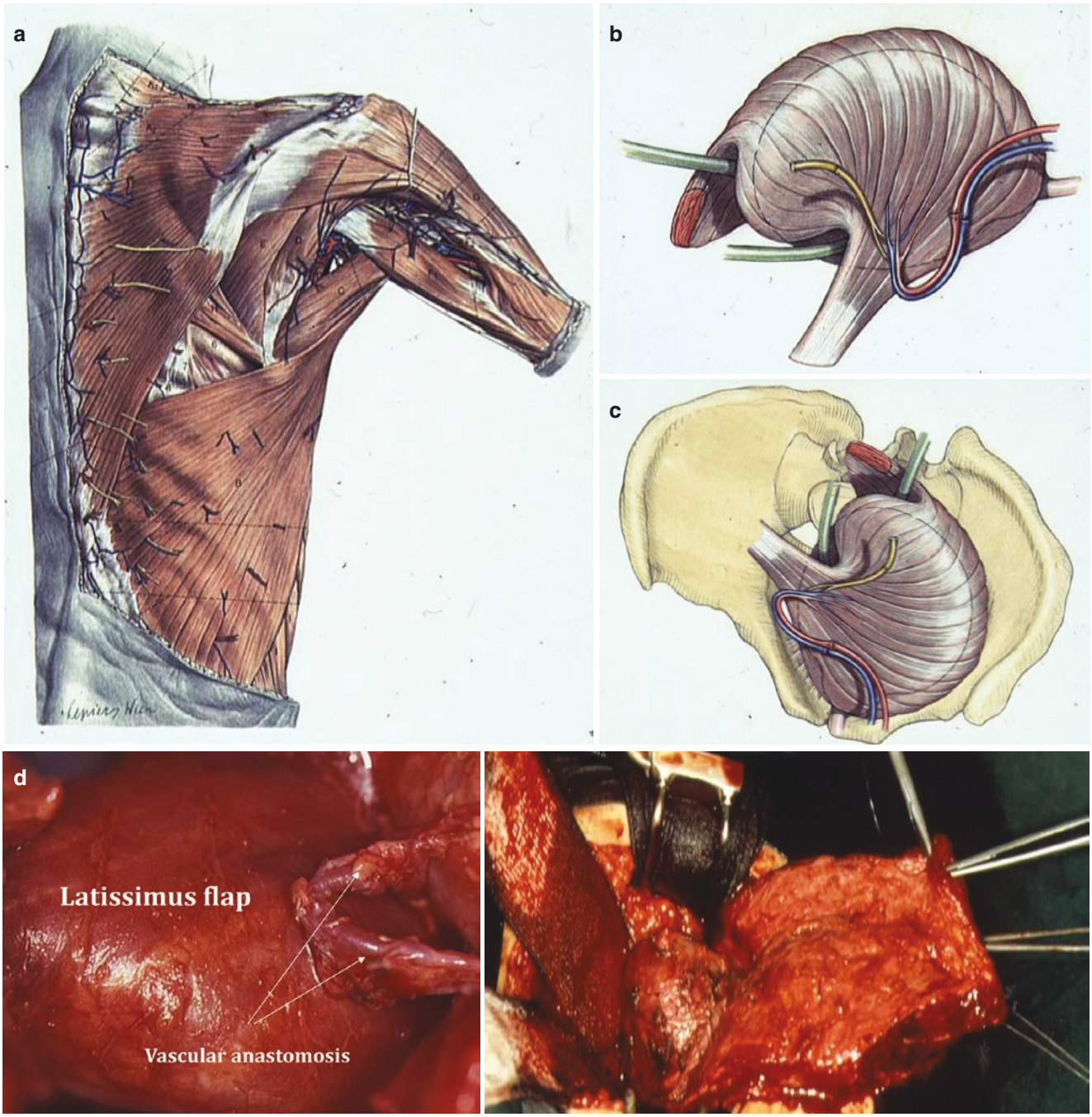

Fig. 40.1 (**a**) Latissimus dorsi muscle before harvesting. Sutures mark original length of muscle. (**b**) Fixation of latissimus dorsi muscle in pelvis (broken line). (**c**) Schematic drawing of position of muscle around bladder with neurovascular connections. (**d**) Final intraoperative aspect of muscle in pelvis with neurovascular connections (right side)

TURP. Of those patients, five voided RV after the initial LDDM surgery and suffered increasing RV. They underwent a TURP with the result of regaining complete voiding afterwards. Another patient who voided with a high residual was able to micturate after the TURP residual free. Also, it remains unclear, if those patients were identical to those with the grade III Clavien complications and did not gain any improvement after the TURP (Tables 40.2, 40.3, 40.4, 40.5, and 40.6).

Overall the LDDM procedure is an option for a specific group of patients with an acontractile detrusor to undergo this procedure. The surgery should be performed in a centres of excellence as these primary published reports have recommended [11, 12]. The success rate lies between 83 and 90%

Table 40.1 Main etiologies for bladder acontractility

Etiology	Number of patients
Spinal trauma	9
Tethered-cord syndrome	4
Lumbar hernia of nuclei pulposi	3
Megacystis and BOO	2
Idiopathic	4
Voiding dysfunction post hysterectomy	1
Sacral myelomeningocele	1

(70% voiding without residual and 12% of 50% voiding). In those who do not void completely after 4 months, a TURB of the prostate or the bladder neck should be performed if there is a sign of any subvesical obstruction. The postoperative complication rate seems to be high with around 37% Clavien Grade III, but related to the invasiveness to the surgery and the possible improvement in QoL acceptable for those patients who want to stop self-catheterisation.

Table 40.2 Preoperative parameters

Patients	Mean age in a (range)	Frequency of CIC/d (range)	PVR in mL (range)	Time of CIC prior to LDDM in a month (range)	Mean number of UTI/a (range)
24	37 (14–63)	5.0[1] (4–8)	486 (250–800)	55 (17–195)	10 (0–24)

SNM sacral neuromodulation, *CV* complete spontaneous voiding postoperatively, *PV* partial spontaneous voiding postoperatively, *NV* no voluntary voiding postoperatively, *preop.* preoperatively, *pat.* patients

Table 40.3 Pre- and postoperative clinical results

Total (n = 24)	Gender ♂:♀	CIC/24 h preop.	CIC/24 h postop.	UTI/a preop.	UTI/a postop.	PVR (in mL) preop.	PVR (in mL) postop.
17	11:6	5.1 (4–7)	0	10.4 (0–24)	0	486 (250–800)	25 (0–100)
3	3:0	5 (4–6)	3.3 (2–4)	7.5 (5–10)	0	400 (300–500)	200 (150–250)
4	2:2	5 (4–6)	4.8 (4–6)	17 (10–24)	2 pat. w/o UTI	583 (400–800)	575 (400–700)

CIC clean intermittent catheterization, *UTI* urinary tract infections, *PVR* post-void residual urine volume, *preop.* preoperatively, *postop.* postoperatively

Table 40.4 Postoperative adjuvant treatment

Total (n = 24)	Specific drug intake (cholinergics, antibiotics)	Functional restrictions of upp. extremity	TUR-P (in days postoperatively)	Patient satisfaction (1-excellent; 6-very bad)	Vesico-renal reflux
17	None	None	5 (38–1609)	1.8 (1–4)	None
3	1 (nitrofurantoine)	None	1 (132)	2 (1–3)	None
4	None	None	2 (202 and 420)	6 (6)	None

Table 40.5 Pre-and postoperative detrusor pressure during voiding and uroflowmetry

Patients	Preoperative max. P_{det} Mean/median in cm H_2O (range)	Postoperative max. P_{det} Mean/median in cm H_2O (range)	Postoperative uroflow Mean/median in mL/s (range)
CV	34.5/31 (0–90; n = 11)	58.4/57 (30–120; n = 7)	22/18.5 (10–50; n = 8)
PV	53.3/25 (15–120, n = 3)	60/60 (60–60, n = 1)	10 (2–13n = 1)
NV	35/35 (20–50, n = 2)	34.7/25 (20–59, n = 3)	–

max. P_{det} maximum detrusor pressure

Table 40.6 Major postoperative complications related to the surgical result of voiding graded according to the modified Clavien-classification for surgical interventions of 2004 [15]

	Number of patients	Number of major complications	DVT	PE	PA	CS	WHD	PS
N	8	9	1	1	3	1	1	2
Grade	–	–	I	II	IIIa (2) IIIb (1)	IIId	IIId	IIIb
CV	5	6	1	–	2	1		2
PV	1	1	–	1	–	–		–
NV	2	2	–	–	1	–	1	–

CV complete spontaneous voiding, *PV* partial spontaneous voiding, *NV* no voluntary voiding, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *PA* pelvic abscess requiring temporary drainage, *CS* compartment syndrome of the non-operated shoulder, *WHD* wound healing disorder, *PS* persistent seroma of the operated shoulder requiring surgical intervention

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Part XIII

Bladder Augmentation/Augmentation Cystoplasty

An Overview of Bladder Augmentation

41

Limin Liao

Bladder augmentation or augmentation cystoplasty (AC) is generally acceptable therapy for a small-volume, high-pressure bladder. The purpose of AC is to increase bladder storage capacity, decrease bladder pressure, improve bladder compliance (BC), protect upper urinary tract (UUT) function, provide continence, resist infection, and offer a convenient method of voluntary and complete bladder emptying. The technique has been in existence for >100 years, and has recently been performed laparoscopically or robotically. Currently, the AC techniques available in clinical practice include intestinal cystoplasty (ileum), colocystoplasty (sigmoid), gastrocystoplasty (stomach), ureterocystoplasty, autoaugmentation (vesicomyotomy), seromuscular augmentation, and tissue engineering cystoplasty.

41.1 History

AC was first reported in dogs in 1888 by Tizzoni and Foggi [1], and in humans by von Mikulicz in 1889 [2]. In 1950, Couvelaire first described AC as a treatment for small contracted tuberculous bladders [3]. The use of different segments of the gastrointestinal tract has been described, as follows: the colon in 1912 by Charghi [4]; the sigmoid by Bisgard in 1943 [5]; the cecum by Couvelaire [3]; the stomach in 1956 by Sinaiko [6]; and the classic detubularized ileal patch by Goodwin in 1959 [7]. In 1993, Bellinger described the ureterocystoplasty technique, in which a detubularized segment of dilated ureter was used to augment the bladder [8]. Auto-augmentation or vesicomyotomy was first described by Couvelaire in 1955 [9]. Specifically, the detrusor layer is incised or excised during auto-augmentation, thus creating a large mucosal diverticulum and increasing the bladder capacity. In the mid-1950s, Shoemaker et al. [10] published a series of investigations on seromuscular AC with reversed demucosalized bowel. In addition to the gastrointestinal tract, other natural tissues, such as free fascial grafts, peritoneum, omentum, and reversed seromuscular bowel grafts, have failed and/or associated with a high rate of complications, and hence abandoned [11]. Clean intermittent catheterization (CIC) was introduced by Lapides [12] in 1972, which contributed to the wider use of AC.

The first attempt to replace a bladder defect using artificial material (biodegradable and alloplastic scaffolds) was reported in 1955 by Bohne et al. [13]. The bladder was replaced with an acrylic mold in dogs, and the histologic evaluation showed a "neobladder" composed of inflammatory and fibrous tissue with a thin urothelial lining [13]. Tissue engineering strategies include the use of unseeded and cell-seeded matrices in bladder regeneration. In 2006, Atala et al. [14] reported the first laboratory-created organ to be transplanted into the human body. This small clinical study [14] established the possibility of using tissue-engineered substitutes for organ replacements in humans.

41.2 Indications

AC has been used for neurogenic and non-neurogenic bladder dysfunction when more conservative interventions (Table 41.1), such as behavioral modification, anticholinergics, type A botulinum toxin (BTX-A), or sacral neuromodulation (SNM), have failed [15]. The principal indication for AC is unacceptable lower urinary tract symptoms (LUTS), such as urinary incontinence (UI), due to a small capacity, poorly-compliant bladder associated with the risk of UUT and UUT deterioration due to high bladder storage pressures (detrusor leak point pressure > 40 cm H_2O) [16]. Based on >200 cases of AC at our center, the principal indications for AC are as follows [17–20]: (1) refractory to anticholinergic therapy, BTX-A detrusor injection, and neuromodulation;

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_41

Table 41.1 The indication for augmentation cystoplasty

	Indications
Congenital neurogenic	Myelomeningocele
	Hemirachischisis
	Tethered spinal cord
	Spina bifida
	Sacral agenesis
	Caudal regression
	Scoliosis
Congenital non-neurogenic	Exstrophy (classic, cloacal, epispadias)
	Posterior urethral valves
Acquired neurogenic	Spinal cord injury
	Spinal tumors
	Myelitis
	Multiple sclerosis
	Pelvic fracture
Acquired non-neurogenic	Overactive bladder or detrusor overactivity
	Ketamine abuse-induced vesicopathy
	Defunctionalized bladder in patients on dialysis
	Idiopathic
Infectious	Tuberculosis
	Schistosomiasis
Inflammatory	Interstitial cystitis
	Radiation cystitis
	Chemotherapy-induced cystitis
Iatrogenic	Intra-operative loss of bladder wall (after extirpative surgery for malignancy)
	Bladder contracture due to suprapubic or indwelling urethral catheterization
	Urinary undiversion

(2) high bladder storage pressures (>40 cm H_2O) or decreased BC (<10 mL/cm H_2O) with or without UUT deterioration; (3) socially unacceptable UI due to detrusor overactivity (DO) or decreased BC; (4) high grade and/or low pressure vesicoureteral reflux (VUR) with UUT deterioration; (5) high degree UUT dilation with ureterovesical junction stenosis; (6) bladder contracture due to some infectious and inflammatory disorders, such as tuberculosis; and (7) serum creatinine (Scr) level significantly decreased after indwelling urethral catheterization (IDUC) in patients with chronic renal failure (Scr >2 mg/dL).

41.3 Contraindications

Relative contraindications to AC include inflammatory bowel disease (Crohn's disease, irradiated bowel, short gut syndrome, bladder tumors, and liver failure) [21]. Significant renal impairment is a controversial relative contraindication; however, renal function may stabilize following AC when bladder dysfunction leads to renal insufficiency [17, 18, 22]. At our center, we prefer IDUC for patients with chronic renal failure as a part of the pre-operative preparation and evaluation; if the Scr level gradually decreases after IDUC, it is more likely to indicate recovery of renal function postoperatively. For the decision-making with respect to AC, we take into account the Scr level, renal cortical thickness, the degree of renal atrophy, the glomerular filtration rate (GFR), and complications associated with chronic renal insufficiency before surgery. Pre-existing renal insufficiency may be exacerbated due to electrolyte abnormalities caused by excessive absorption by the bowel mucosa within the urinary tract. Although chronic renal failure is not an absolute contraindication, patients who have a very high Scr level, a low GFR, severe atrophy of the kidney, and renal anemia and/or renal hypertension usually have a poor long-term outcome [17, 18].

41.4 Choice of Tissues/Materials for AC

41.4.1 Gastrointestinal Tract

Different parts of the gastrointestinal (GI) tract from stomach-to-sigmoid have been used for AC, each with strengths and shortcomings.

Ileum. The ileum is the most widely used bowel segment for AC [15]. The ileum is large, mobile, easily available, easy-to-handle, well-defined, has an extensive mesentery, and a rich blood supply; however, ileocystoplasty easily leads to metabolic disturbances (lipid malabsorption, including vitamins A, D, E, and K) and vitamin B12 deficiency (anemia). It has been reported that taking 25–40 cm from the ileocecum maybe reduce the risk of such metabolic disturbances [15]. The incidence of bowel obstruction is more common than colon, while the lack of bile salt reabsorption (diarrhea) and metabolic acidosis are relatively high. In addition, the ileum might not be appropriate in situations in which the mesentery is short, or in patients with significant adhesions, a history of small bowel resection, or a history of pelvic radiation therapy [23]. For women, ileum mesentery may cover the uterus during AC, and cesarean section can be difficult.

Colon. The colon is considered to be an alternative to the ileum for AC. The sigmoid has some advantages, including the thick muscular wall, proximity to the bladder, large lumen, and abundant mesentery; thus, the sigmoid will guarantee adequate capacity and maneuverability for the bladder and have less of an effect upon bowel function than ileocystoplasty [24]. The disadvantages of the sigmoid include larger amounts of mucus, bacterial colonization with a higher risk of UTI and stone formation, and the potential to develop a malignancy [25, 26]. For those patients with neurogenic bowel dysfunction, resection of the sigmoid colon usually results in improvement of refractory constipation; the sigmoid maybe a more attractive choice than the ileum [18, 27]. For women of child-bearing age, the sigmoid mesentery

does not directly cover the uterus during AC, thus, cesarean sections are not impacted. Therefore, the "clamshell" sigmoid cystoplasty is the first choice at our center.

In addition, the caecum is most commonly used in conjunction with the terminal ileum used as a channel which can be catheterized [28]. The ileo-caecal valve is competent to provide continence; however, patients who undergo this procedure are more susceptible to malabsorption and diarrhea [18, 29]. At our center, we perform ileocecal cystoplasty and the Mitrofanoff procedure with the appendix as a channel which can be catheterized [17, 18].

Stomach. Gastrocystoplasty is an alternative when the bowel is unavailable or unsuitable. Advantages of the stomach include less mucus production, a lower incidence of bacteriuria, and a rich blood supply, but use of the stomach for AC has declined significantly due to disadvantages, such as debilitating hematuria–dysuria syndrome, risk of bladder ulcers and perforation, vitamin B12 malabsorption, and severe disturbances to the abdominal cavity [30].

Jejunum. The jejunum has nearly no use for AC due to significant disadvantages, including severe electrolyte abnormalities, risk of profound dehydration, and iron and calcium deficiencies.

41.4.2 Ureter

Because of the natural characteristics of the ureter (elasticity, smooth muscle, and urothelium), the ureter is a good material for augmentation [31]. A pre-existing dilated ureter is used for augmentation of the bladder during ureterocystoplasty, and is usually opened to form a ureteric patch [31]. The ureter has also been used for AC before renal transplantation [15]. The advantages of the ureter include a urothelial lining without mucus production, lack of electrolyte abnormalities, and no need for bowel resection. The disadvantages of the ureter are the limited gain in capacity and availability, and the occasional need for a nephrectomy.

41.4.3 Auto-Augmentation

The detrusor layer is incised or excised during auto-augmentation (vesicomyotomy/vesicomyomectomy), thus creating a large mucosal diverticulum to increase bladder capacity and compliance [26]. It has been suggested that this technology provides unsatisfied efficacy, so the technique has rarely been reported in recent years [23]. The advantages of the ureter are the urothelial lining without mucus production, lack of electrolyte abnormalities, and no need for a bowel resection. The disadvantages of the ureter include the limited gain in capacity and compliance, technically-demanding use, and risk of perforation.

41.4.4 Seromuscular Augmentation

During a seromuscular colocystoplasty, the exposed urothelium is covered by colonic submucosa, and is more technically demanding than an intestinal cystoplasty [10]. The advantages of seromuscular augmentation include a urothelial-lined augmentation without mucus production and lack of electrolyte abnormalities. The disadvantages of a seromuscular augmentation are the limited gain in capacity and compliance, and the more technically-demanding procedure.

41.4.5 Tissue Engineering

The search for some material that might serve as an "off the shelf" bladder substitute has been ongoing since the turn of the century. These studies can be divided into the following two groups: artificial materials designed to replace resected tissues; and absorbable materials designed to act as a scaffold for bladder healing, with eventual replacement by host tissue. Tissue engineering has made tremendous progress since the early 1990s. Current bladder tissue engineering modalities include unseeded (cell-free matrix) and seeded (cell matrix) scaffold strategies. Recent studies have successfully used bladder tissue engineering for ACs in patients with NB using host autologous mature urothelial/smooth muscle cells seeded onto scaffolds with subsequent omental wrapping of the augmentation to improve vascularity of the graft or resorting to SIS as acellular tissue matrix-based scaffolds to regenerate functional bladder tissue [14, 32]. The outcomes of the aforementioned techniques, such as bladder capacity and compromise, are satisfactory. The most serious shortcoming in tissue engineering is the significant risk of graft ischemia, patch contraction, diminished capacity, and increased pressure; how to resolve these problems warrant additional study.

The use of SIS in clinical practice has been reported by our group [33]. A double patch in three of eight individuals was used according to the pre-operative size of the bladder to achieve a sufficient volume. Regardless of the size of the patch, there was no difference in total bladder capacity, maximum detrusor pressure, or compliance after a 1-year observation period. Promising results have been noted previously with polyglycolic acid and other materials, as well as with seeded and non-seeded scaffolds, only to find later that the patches were contracted, the capacity was diminished, and the pressures were increased, leading to the necessity of an enteric augmentation. We continue to provide meticulous follow-up of the cohort for several more years to determine if these moderate-term favorable results are maintained [33]. Whether or not non-seeded scaffolds are a better long-term source than cell-seeded constructs has not been established. The advantages of SIS are urothelium-lined augmentation

without mucus production and a lack of electrolyte abnormalities, theoretically unlimited donor tissue. The disadvantages of SIS are the limited gain in capacity and compliance, long-term outcomes, experimental nature, and the requirement for laboratory expertise.

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Bladder Autoaugmentation

42

Pawan Vasudeva

42.1 Bladder Autoaugmentation

Bladder augmentation is sometimes required for a poorly compliant bladder and/or a bladder with small capacity unresponsive to conservative measures. While augmentation with gastrointestinal segments is considered gold standard from an efficacy standpoint, it is associated with significant morbidity. Since much of the morbidity is related to gastrointestinal segment interposition in the urinary tract, various other alternative techniques like autoaugmentation have been described.

Autoaugmentation is based on the principle of surgically creating a large mouthed urothelium lined bladder diverticulum (Fig. 42.1). This may be achieved by a detrusoromyotomy or detrusorectomy. The aim of autoaugmentation is to produce a pressure sink by converting a part of the bladder into a yielding section so as to improve compliance and capacity.

The term "autoaugmentation" was coined by Cartwright and Snow and their original description of the technique involved a partial detrusorectomy [1]. They reported excellent initial results in five of seven patients undergoing autoaugmentation [2]. Since then, various technical modifications have been proposed. Hansen et al. utilized only detrusor myotomy without detrusor myectomy achieved by a coronal incision from the bladder on one side through the dome of the bladder to the other side. To prevent myotomy closure, they sutured anterior and posterior detrusor flaps to the anterior rectus muscle and the retroperitoneum, respectively [3]. Detrusor from atleast half of the bladder to approximately two third of the bladder has to be removed for a significant large mouth bladder diverticulum to form [4]. Laparoscopic and robotic autoaugmentations have also been described [5, 6].

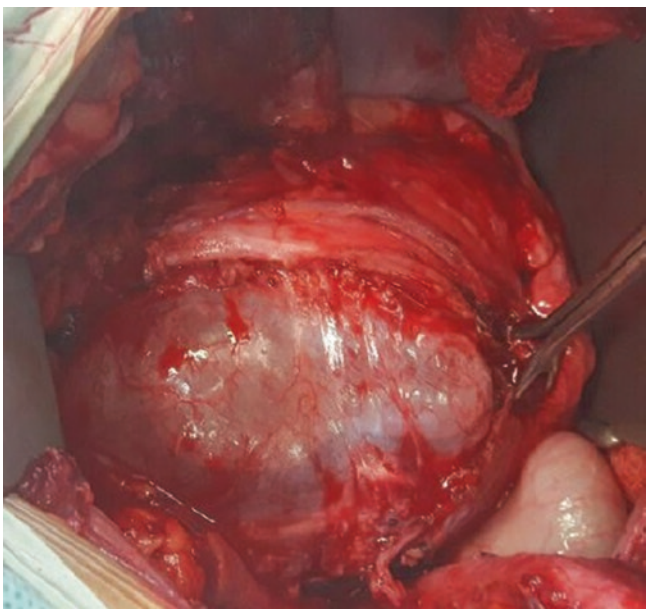

Fig. 42.1 Bladder autoaugmentation: an anteroposterior detrusorotomy and creation of a wide mouthed diverticulum in progress

42.1.1 Autoaugmentation in Paediatric Neurogenic Bladder

Literature search shows discordant long term efficacy data in so far as autoaugmentation in the paediatric neurogenic bladder population is concerned. Hansen et al. reported encouraging long term results from their series of 25 paediatric patients with neurogenic bladder who underwent detrusor myotomy. With a median follow up of 6.8 years, they noted statistically significant and progressive improvement in bladder capacity and compliance. Kidney function developed normally in all but one patient, reflux was alleviated in seven of nine cases and 18 patients had become continent on clean intermittent catheterization. Four patients subsequently required an enterocystoplasty [3]. Other authors have also reported good long term results with paediatric bladder autoaugmentation [7–9].

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In contrast Marte et al. reviewed their results of autoaugmentation done for 11 paediatric MMC patients, all having poorly compliant bladders. At a mean follow up of 6.6 years, the procedure had failed in seven, of which five underwent an ileocystoplasty [10]. McNeily et al. reported result of detrusor myotomy done in 17 paediatric MMC patients with neurogenic bladders. At a median follow up of 75 months, 71% patients (12/17) were considered clinical failures because of upper tract deterioration and/or incontinence. Ninety three percent patients (14/15) were considered urodynamic failures on the basis of persistent poor compliance and/or less than expected gains in safe bladder capacity [11].

42.1.2 Autoaugmentation in Adult Neurogenic Bladder

Similar to the paediatric patients, efficacy results are equally discordant for autoaugmentation in the adult neurogenic bladder population. Strohrer et al. reviewed their results of autoaugmentation done in 50 adult patients, majority being neurogenic bladder patients. Results were reported for those who had a minimum follow up of 6 months and had achieved a stable condition. The maximum cystometric capacity and detrusor compliance increased significantly and the voiding pressure decreased significantly. With the exception of five failures, all patients had substantial improvement, both subjectively and objectively. The authors concluded that autoaugmentation is therapy of choice before enterocystoplasty for low capacity high pressure bladder refractory to medical management [12]. Veenboer et al. compared detrusorectomy and enterocystoplasty in 47 adult spina bifida patients (26 detrusorectomy, 21 enterocystoplasty) with a median follow up of 13.1 and 15.3 years, respectively. Four vs. zero patients need reoperation in detrusorectomy and enterocystoplasty group, respectively. Though, preoperative bladder capacity was higher in detrusorectomy group, increase in capacity was significantly more in enterocystoplasty group (300 vs. 77.5 mL, $p = 0.006$). Other parameters including compliance, end filling pressure and continence rates showed similar results between the two groups. They concluded that detrusorectomy may be preferable to enterocystoplasty provided that the bladder capacity is sufficient [13].

Unfortunately, other authors have not been able to reproduce favourable results with this procedure. Kumar and Abrams reported a high failure rate in their series of adult patients who underwent autoaugmentation. Of the six NDO patients who underwent autoaugmentation, four had to undergo an enterocystoplasty subsequently due to persisting NDO [14]. Leng et al. reported comparison of detrusor myectomy and enterocystoplasty in (1) 16 patients of MMC and (2) 11 patients with neurogenic bladder dysfunction. Of patients with MMC, 11 initially underwent a detrusor myectomy and out of them only five patients exhibited satisfactory urodynamic improvement. The rest six patients required subsequent enterocystoplasty. Of 11 patients who underwent an enterocystoplasty (five primary and six secondary) all had significant improvement in bladder capacity and compliance. Of patients with neurogenic bladder dysfunction, four detrusor myectomies and eight enterocystoplasties were performed. Of four myectomies, one was converted to enterocystoplasty after postoperative urodynamics failed to show improvement on compliance. Though, urodynamic improvement was seen in 3/4 myectomy and 8/8 enterocystoplasty, symptomatic improvement was seen in 2/4 myectomy and 7/8 enterocystoplasty [15].

Various factors have been attributed for the conflicting efficacy results. The most accepted explanation for poor results is mucosal shrinkage in early postoperative period because of bladder drainage or ischaemia of the diverticulum leading to fibrosis in late postoperative period.

Cartwright believes that fairly immediate distention of the autoaugmentation segment postoperatively is essential to prevent scarring and contraction. For this, intermittent vesical filling to a predetermined pressure/capacity is desirable. Unfortunately, no data is available on what is the optimum regimen, pressure and volume for intermittent bladder filling [16]. Rocha has proposed an inflatable silicone balloon bladder conformer as an alternative to bladder cycling to prevent mucosal shrinkage [17]. Other authors have tried covering the autoaugment with demucolized flaps, rectus muscle, omental flaps, peritoneal flaps etc. to support the autoaugmentation with variable results.

Another factor which may influence results is patient selection. Since autoaugmentation more effectively lowers pressure than it increases capacity, authors believe that the procedure may be more suitable for patients with a fairly good preoperative bladder volume. A threshold of 50–80% of expected bladder capacity is suggested in deciding candidates suitable for autoaugmentation [3, 4, 13]. The cut off is however arbitrary and a randomized study is required to clarify the threshold value.

42.2 Complications of Autoaugmentation

One thing on which there is uniform consensus among authors is that autoaugmentation is associated with much less short and long term morbidity when compared to an enterocystoplasty. Leng et al. reported a complication rate of 3% for autoaugmentation in contrast to 20% for enterocystoplasty [15]. Bladder rupture risk may potentially be a little more with autoaugmentation than with an enterocystoplasty as the bladder rupture pressure was shown in an experimental animal study to be slightly lower after a detrusorectomy than after an enterocystoplasty [18].

To summarize, while autoaugmentation is very attractive from a low surgical burden and a low morbidity standpoint when compared to enterocystoplasty, the inconsistency of success when compared to established efficacy of enterocystoplasty make it a less favoured option. Considering that it does not preclude a subsequent enterocystoplasty, it may be an acceptable alternative in highly selective cases.

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Augmentation Cystoplasty

43

Homero Bruschini, Pawan Vasudeva, and Limin Liao

43.1 Enterocystoplasty

Homero Bruschini

43.1.1 Introduction

The intention to create a good low pressure reservoir is fully accomplished with detubularized intestinal segment. Ileum, colon and cecum can be used. Facilities favor the use of ileum, which represent the majority of cases published. It is easy to remove, is close to the bladder and may be shaped easily into a reservoir [1]. Also, reconstitution of intestinal transit seems to be less problematic at the ileum. The intestinal segment needs to be long enough to be fashioned close to a spherical form [2, 3] and to create a volume consistent with patient's requirements (Fig. 43.1). Care should be taken to avoid tension at the mesentery blood supply to the intestinal segment, in order to prevent ischemia. Mobilization of the segment to the bladder should always be checked before intestine excision, mainly in reoperations. Colon or ileum can either be chosen at the time of the surgery, according to this convenience.

Bladder preparation includes incision in the anterior/superior/dome surfaces either in transverse or sagittal plane, mimicking an open clam. This makes a good extension length for anastomosis with the detubularized loop. The clam cystoplasty is the most common form of bladder augmentation.

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Attempts to reduce mucus secretion and reduce the reabsorption of urine by the intestinal mucosa produced some technical variations, not developed and tested extensively until now [1]. Seromuscular colocystoplasty involves removing the detrusor and leaving the bladder mucosa denuded. This area is then covered with a demucosalized sigmoid patch [4, 5]. The mucosa is surgically removed from the intestinal segment or destroyed by argon beam [6].

Vesicoureteral reflux (VUR) management should be considered at the time of augmentation. There is a predominant opinion that improvement of bladder compliance and decrease of bladder pressure precludes the need for ureteral reimplantation [1] with a resolution of 85% for VUR excluding grade V [7]. Reimplantation should still be considered in patients with recurrent febrile UTI [8] or in grade V reflux [9].

43.1.2 Results

The fifth International Consultation on Incontinence (fifth ICI) [1] reviewed the main series for patients with neurogenic bladder submitted to augmentation, in a total of 762 patients. The segments used were ileum, sigmoid, colon and caecum. Peri-operative mortality ranged between 0 and 3.2%. Prolonged post-operative ileus was the most frequent morbidity, up to 11.7%. Continence status was cured/improved in 40–95% of the cases. Szymanski et al. [10], studied the impact of urinary and faecal incontinence status on quality of life of children with spina bifida. They found health related quality of life lower with an increasing amount of urinary incontinence. In this fifth ICI revision, only three series reported effect on quality of life. Excellent/good results on QOL was found in 89.8% [11], 83% [12], 92% [13] of neurogenic bladder patients submitted to augmentation.

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_43

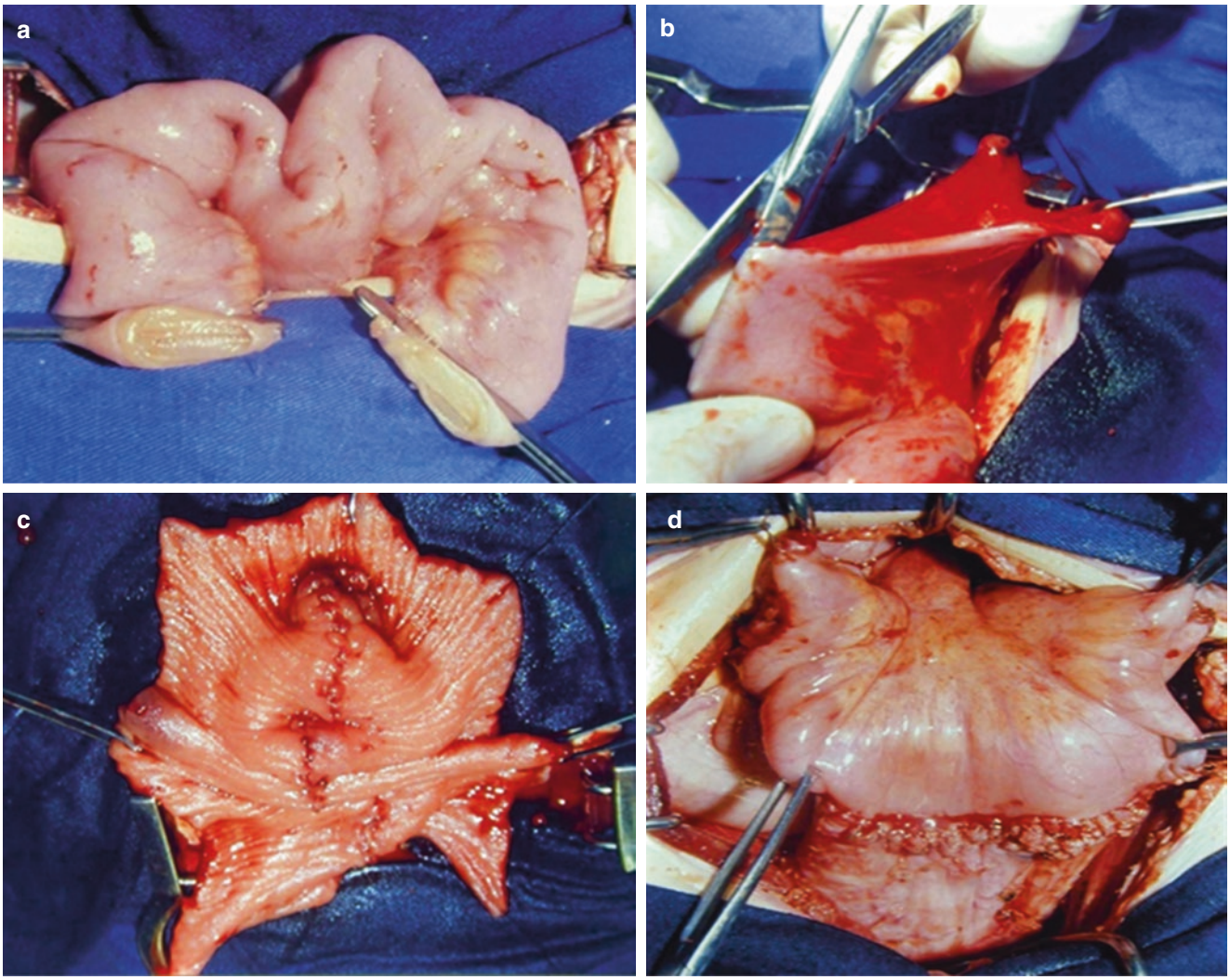

Fig. 43.1 Clockwise: (**a**) ileum segment isolated; (**b**) opening the contra-mesenteric border; (**c**) starting sutures to reconfigure the volume shape; (**d**) sutures and anastomosis completed

43.1.3 Risk of Neoplasia

The consensus today is that augmented bladder has higher risk of developing tumors than the matched population, but this risk has not been yet defined [1]. Most series of bladder augmentation group together cases of exstrophy, posterior urethral valves and spina bifida, making individual conclusions difficult [14, 15]. Higuchi et al., reviewing 153 patients with augmented bladders, found no difference ($p = 0.54$) in the incidence of bladder cancer in patients with augmentation cystoplasty (seven patients [4.6%]) vs. controls (four patients [2.6%]) [15]. The usual location for adenocarcinomas is the junction of the intestinal mucosa with the urothelium (Fig. 43.2). The most common tumors are transitional cell carcinomas and adenocarcinomas, with occasional cases of desmoid tumors [16] and tuberous adenoma [17] (Fig. 43.3). Neoplasia is unlike to occur in the first decade after augmentation. Soergel et al. [18] reported mean time of 19 years from augmentation to occurrence of transitional cell carcinomas. All these tumors have high mortality rate and early diagnosis is essential but routine screening has not been shown to reduce mortality [19, 20]. Even when annual cystoscopy is used, patients have been demonstrated to develop lethal bladder cancer. Based on this, Loftus et al. [21] suggest cystoscopy or upper tract investigation for episodes of hematuria in all neurogenic bladders and in colon-containing reservoirs after age 50 and then every 2–3 years. Kokorowski et al. [22], did a cost-analysis on post-augmentation malignancy and cost estimates from published reports or US government sources. They concluded that annual screening with cytology and cystoscopy will only be cost effective if the annual rate of cancer development were more than 0.26%, what is not the present situation.

In a way to predict the predisposition to tumor formation, Ivil et al. [23] investigated genetic instability (in the form of

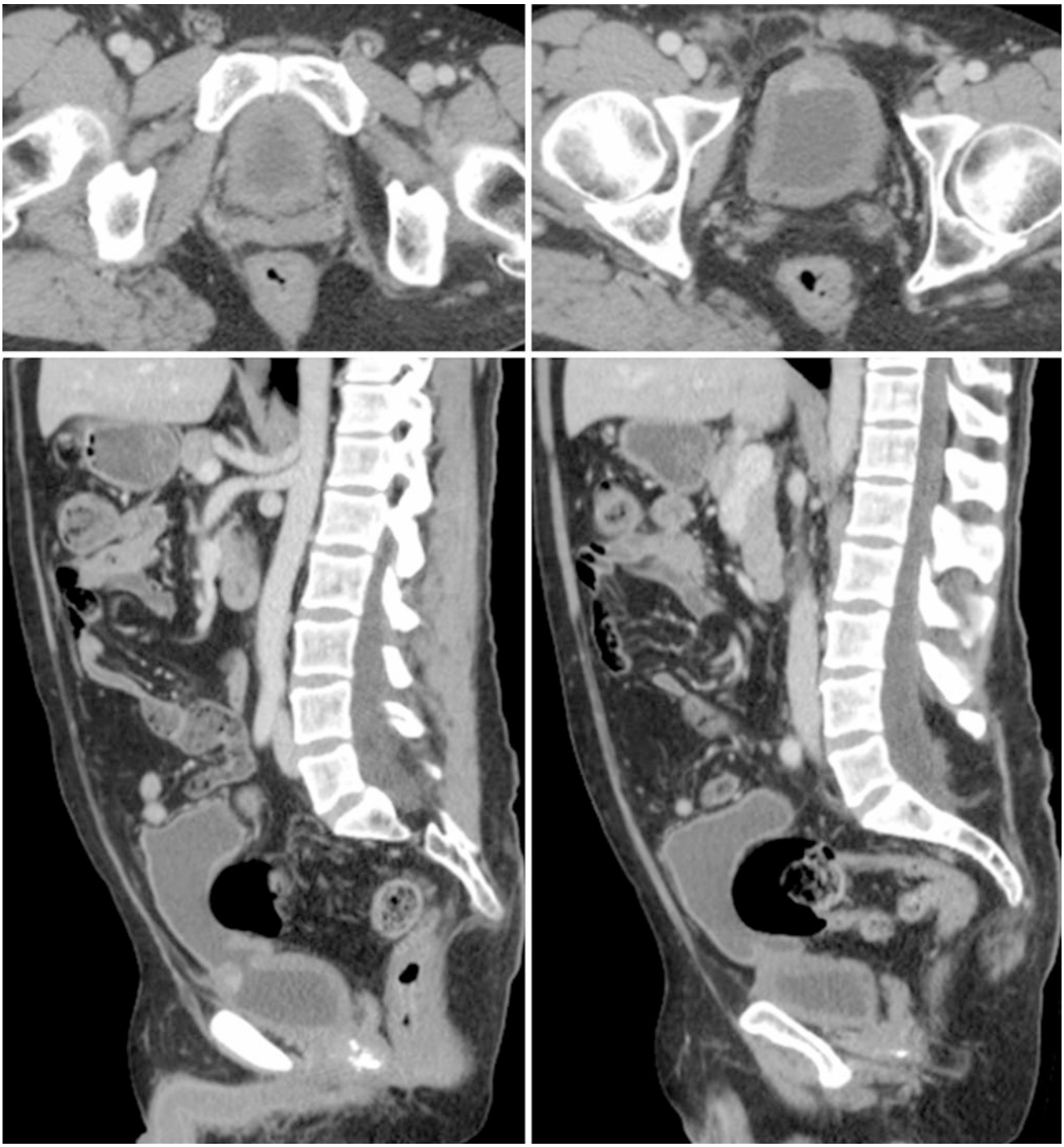

Fig. 43.2 CT Scan of patient with hematuria and bladder augmentation (ileum) done 22 years before. A tumor can be seen at the bladder-intestine transition

numerical chromosomal aberrations) at the enterovesical anastomosis in patients who had undergone a clam ileocystoplasty using fluorescent in-situ hybridisation (FISH). Chromosomal numerical abnormalities occur at the enterovesical anastomosis following a clam ileocystoplasty and chromosome 18 appears to be a particularly good marker of genetic instability. The results of this study indicate that morphologically normal tissue obtained from the enterovesical anastomosis displays evidence of chromosomal instability that may predispose to tumor formation, but further studies are necessary to determine if FISH patterns predict the presence or absence of tumor.

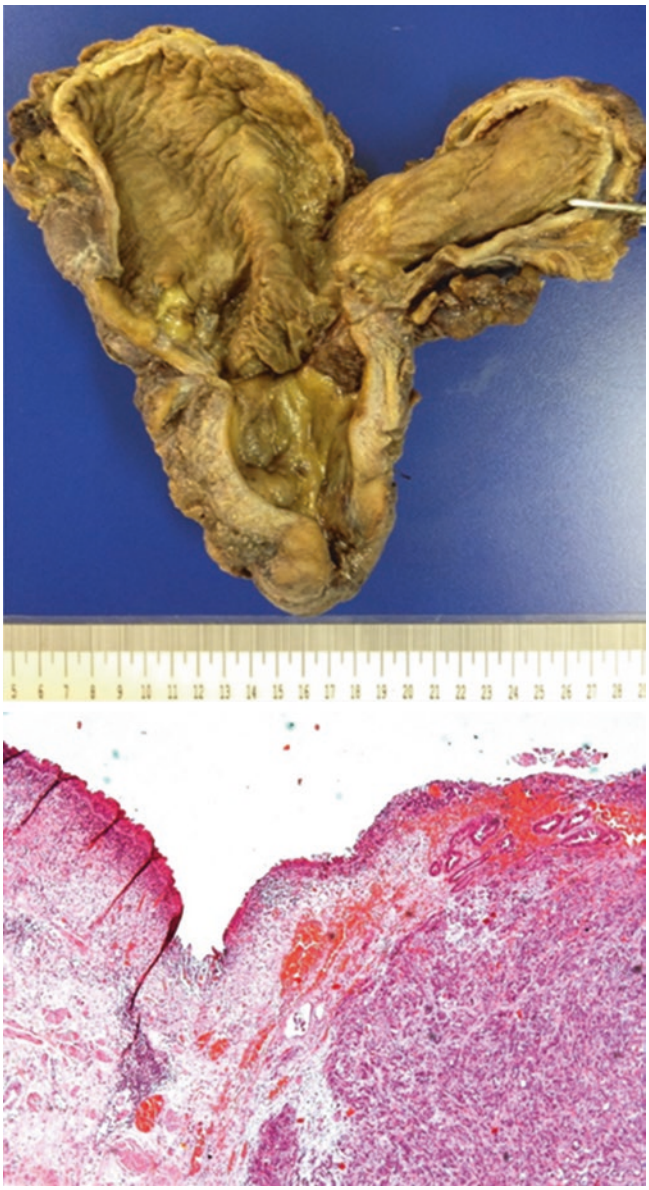

Fig. 43.3 Product of cystectomy with tumor at transition between ileum and bladder. Microscopy shows adenocarcinoma at the site of anastomosis

43.1.4 Complications

Cystoplasty perforation is the more severe complication to occur in these patients, with possible lethal consequences no matter the intestinal segment used [24]. It usually occurs at the junction of the bladder with the intestinal segment used to augment the reservoir [1]. Eventually, traumatic catheterization or urodynamic manipulation can promote perforation [25]. High pressures of course can lead to ruptures, but high distensions can cause ischemia of the wall and fragilities to the less vascularized area, the bladder-intestine anastomosis, what promote perforations. This can be minimized by making an augmentation with a final volume safety above the usual volume between catheterizations. Perforation is supposed to occur in 5–13% of the cases [26]. It is a urological urgency and laparotomy to evacuate urine, suture perforation and drain the cavity is mostly mandatory.

Stephany et al. [27], in a retrospective 10-years case control study of 52 patients, concluded that patients with neurogenic bladder are itself at increased risk for urinary tract stones. Augmentation add new predisposition to lithogenesis as mucus production. Bladder calculi are increasingly recognized as a complication of bladder augmentation, affecting 11–52% of patients and usually requiring an operative procedure [28–33]. Szymanski et al. [33], found recurrence rate in 47.7% of patients (median recurrence time 9.5 years after first surgery), no matter open or endoscopic treatment or after fragmentation or removing calculi intact (Fig. 43.4). Although open cystolithotomy or endoscopic management is treatment alternative for bladder stones, endoscopy via urethra carries the risk of damaging the urethra in some patients. Yet, residual fragments left in the bladder after stone fragmentation can become a nidus for bladder stone recurrence. Therefore, treatment should be individualized according to patient's conditions and equipment facilities. Patients with high recurrence of bladder stones can empirically perform periodic bladder lavages with saline.

Theoretically, the use of the distal ileum exposes the patient to a vitamin B12 deficiency but this problem is rarely seemed clinically. Patients, mainly children, should be periodically checked for the presence of megaloblastic anemia. Rosembaum et al. [34], in a review of a large group of patients submitted to augmentation during childhood, found that patients are at the highest risk beginning at 7 years postoperatively, and the risk increases with time. They recommend an annual serum B12 value in children beginning at 5 years following bladder augmentation. Urine resorption by the intestinal mucosa can lead to hyperchloremic acidosis in up to 15% of cases [1]. Possible anomalies in calcium metabolism do not appear to have interference in children growth, but the subject is still under debate [1, 35]. Special care should be directed to patients with decreased creatinine clearance, since metabolic acidosis is not fully compensated [2].

After bladder augmentation, intestinal transit disorders may occur and is probably underestimated. Somani et al. [36] reported a high rate of intestinal disorders affecting nearly 50% of patients treated for neurogenic bladders and 10% are really distressed by this problem. The fifth ICI [1] suggests patient should be informed of this risk before surgery. Metcalfe et al. [32] reviewed the records of the first 500 bladder augmentations performed from 1978 to 2003 at their institution in a mean follow-up of 13.3 years. Of the patients 16 (3.2%) required laparotomy for bowel obstruction and 47 (9.4%) required repeat augmentation. While the requirements for additional surgery are not trivial (34%), 66% of

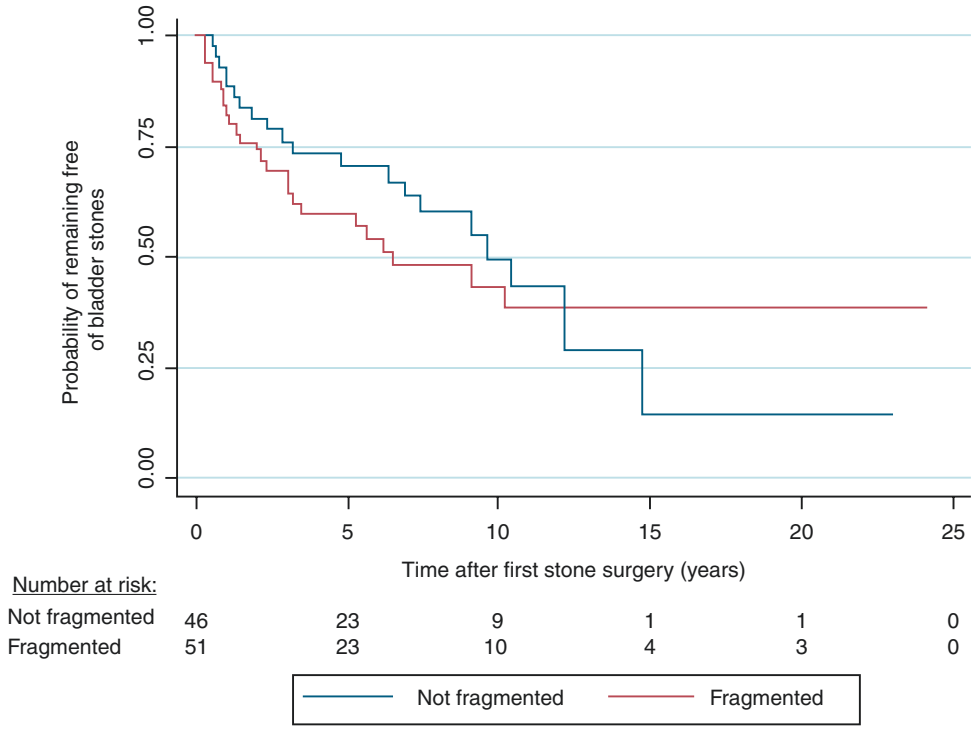

Fig. 43.4 Kaplan-Meier estimative of patients remaining stonefree after first stone surgery stratified by stone fragmentation. Blue line represents unfragmented stones. Red line represents fragmented stones. (Szymanski KM, Misseri R, Whittam B, Amstutz S, Kaefer M, Rink RC, Cain MP. Cutting for stone in augmented bladders: what is the risk of recurrence and is it impacted by treatment modality? J Urol. 2014;191:1375–1380 [33])

their patients have not required any further surgery in the augmented bladder during this follow-up.

Chronic bacteriuria is the rule with intermittent catheterization and only could be considered a problem in the presence of functional or anatomic disorders of the reservoir [1] or with clinical symptoms. There is a consensus about treating bacteriuria in pregnant women and those with bladder augmentation are not an exception. Equally, individuals with ureteral calculi and those who will undergo invasive urological procedures should be submitted to antimicrobial prophylaxis. Nevertheless pyuria itself is not an indication for therapy, it should be elected for treatment when accompanied by fever, bleeding without other causes or bacteraemia.

43.2 Gastrocystoplasty

Pawan Vasudeva

43.2.1 Introduction

Bladder augmentation is sometimes required for a poorly compliant bladder and/or a bladder with small capacity unresponsive to conservative measures. While enterocystoplasty is most commonly used, interposition of small/large bowel has its own morbidity. Gastrocystoplasty, the use of vascularized segment of stomach for bladder augmentation, is an alternative with its own pros and cons. Leong reported on the use of stomach in bladder reconstruction way back in 1978, but it was not until Adams et al. published their encouraging results that this procedure began to be widely used [37].

43.2.2 Surgical Technique

The surgical technique of gastrocystoplasty was described by Adams et al. in 1988 [38]. It involves a midline abdominal incision. The size of stomach wedge isolated is individualized but the greatest width of the wedge at the greater curvature is generally 7–10 cm. Antrum is avoided and incisions into the stomach should stop well short of the lesser curvature since a vagotomy could interfere with gastric emptying. The stomach wedge is isolated and mobilized on its vascular pedicle based either on right gastroepiploic or left gastroepiploic artery. Following closure of the stomach in two layers, the gastric patch is brought to the pelvis through a window in the transverse mesocolon. Bladder is bivalved anteriorly from just proximal to bladder neck through the dome posteriorly to interureteric ridge and the gastric patch is anastomosed to the bivalved bladder (Figs. 43.5, 43.6, 43.7 and 43.8). Raz et al. used a GIA stapler to harvest the gastric segment for augmentation without opening the stomach, which may potentially decrease blood loss and operative time [39]. Laparoscopic gastrocystoplasty has been described by Docimo et al., though not much literature is available on the subject [40].

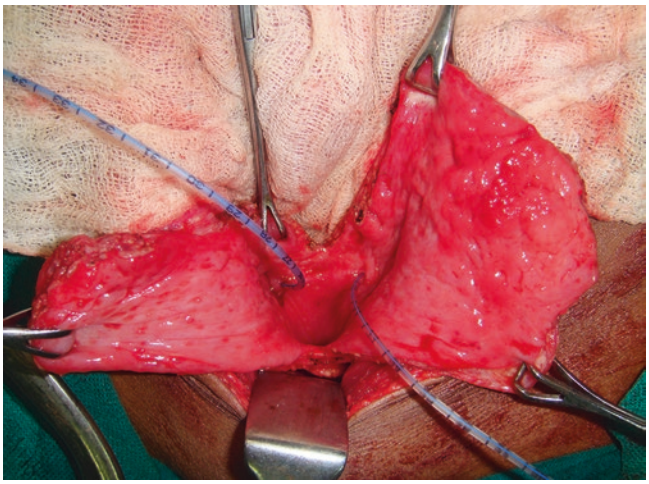

Fig. 43.5 Bladder bivalved anteroposteriorly with infant feeding tubes in both ureters

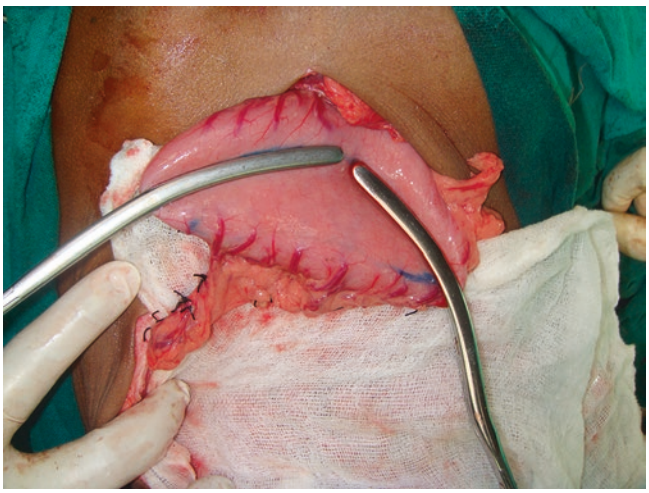

Fig. 43.6 Gastric wedge selected based on right gastroepiploic artery

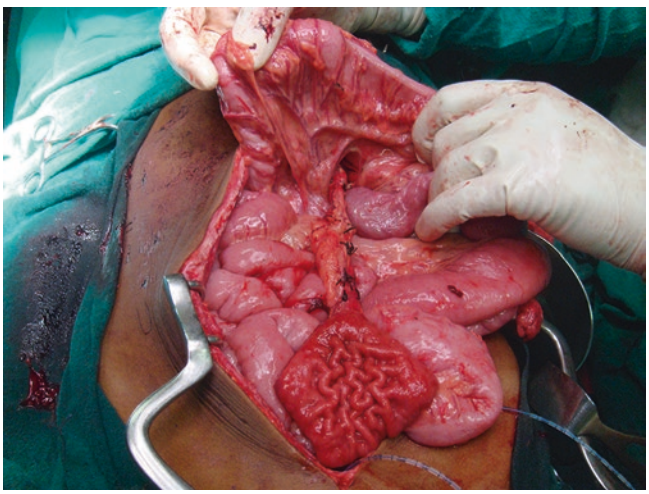

Fig. 43.7 Gastric patch brought to pelvis through a window made in transverse mesocolon

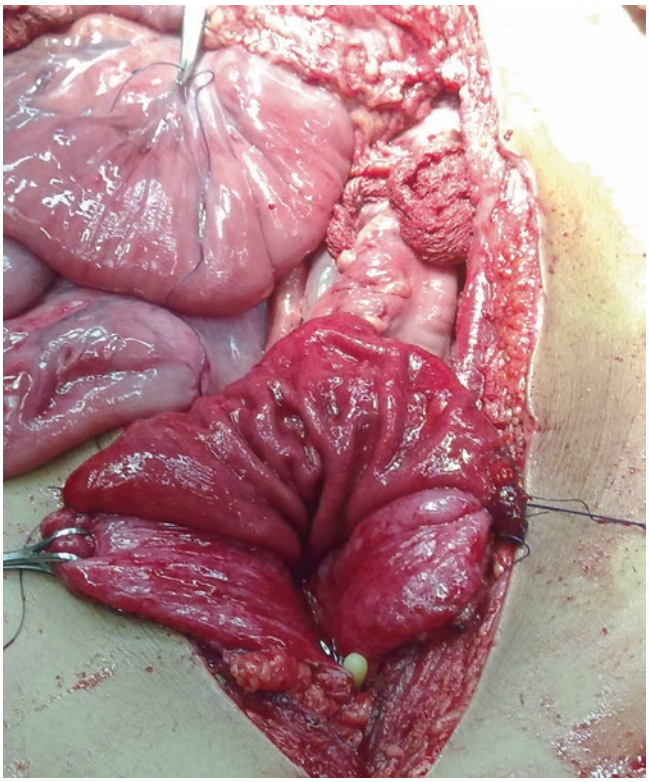

Fig. 43.8 Anastomosis of gastric patch to bivalved bladder in progress

43.2.3 Efficacy

While majority of the data on gastrocystoplasty is from the pediatric population, encouraging results in the adult population have also been published. Most studies are of mixed population of patients e.g. patients with neurogenic bladder, cloacal exstrophy, posterior urethral valves etc. and so the results must be interpreted in that context.

Adams et al. reported their results of 13 patients (five had neurogenic bladder) who underwent bladder reconstruction with gastric segment. The average age was 6.4 years and average follow up period was 13 months. All patients had stable upper tracts radiographically and stable or improved renal function. Nine patients were totally reliant on CISC for emptying. Eleven patients were completely continent [38].

Leonard et al. reported results of 23 patients with a mean age of 10 years who underwent a gastrocystoplasty. Neurogenic bladder was the indication in 15 patients and the mean follow up period was 45 months. They observed stable or improved upper tracts in 18 of 21 patients and socially acceptable urinary continence in 19 of 21 patients who maintained a gastrocystoplasty (one had a composite augment with ileum). Two patients voided spontaneously while 19 required CISC for emptying [41].

Sheldon et al. in their series of 23 patients with median age of 4.5 years who underwent bladder reconstruction with gastric segment also found the procedure to be highly effective in the pediatric population in so far as protecting the upper tracts and achieving continence was concerned [42].

Hubert et al., in their series of 35 patients (17 had neurogenic bladder) who underwent a gastrocystoplasty, with median age of 9.4 years and median follow up of 19 years, reported that majority of patients with normal/mildly impaired preoperative renal function had stable/improved renal function on follow up. In contrast, half of those with preoperative renal insufficiency had continued deterioration postoperatively [43].

Azim et al. reviewed their results of gastrocystoplasty done for areflexic low compliant neurogenic bladder in 30 patients (age: 23.4 ± 11 years). The etiology of neurogenic bladder was MMC in 26 and spinal cord injury in 4 patients. At a mean follow up of 2.9 years, all patients were satisfied with the results. The renal function remained stable or improved in 29 patients while one patient with a preoperative serum creatinine of 4.5 mg/dL continued to deteriorate slowly and ultimately required hemodialysis. The mean bladder capacity, compliance and end filling pressure improved from 115.5 to 375 mL (225% increase), 1.5 to 10.3 mL/cm of H_2O and 72 to 37 cm of H_2O (52% reduction), respectively. Nineteen patients voided spontaneously while 11 required CISC for emptying. Continence was achieved in 25 patients with augmentation alone, 4 required an artificial urinary sphincter (same sitting) and one patient remained incontinent as sphincter was not applied due to young age of the patient [44].

Singla and Galloway reported results of 22 patients (14 augmentation gastrocystoplasty, eight continent gastric urinary reservoirs). The mean age was 44 years, neurogenic bladder was the indication of surgery in 11 patients and the mean follow up period was 9.8 months. They observed improvement in renal function in all except one patient in whom serum creatinine increased from 4.5 to 6.4 mg/dL postoperatively. In 14 patients with preoperative urodynamic confirmed low bladder capacity (mean 150 cc) and low compliance, postoperative urodynamic study revealed improvement in both capacity (mean 450 cc) and compliance. Five voided spontaneously while 17 required CISC for emptying. Complete continence was achieved in all patients [45].

Overall, gastrocystoplasty is clearly an effective procedure for improving bladder capacity and compliance. While the improvement in compliance is similar to small/large bowel, studies have shown that the increase in capacity may be a little lesser with the gastric patch when compared to the small/large bowel [46]. Although variable amount of gastric patch harvest may in part explain this, less volume expansion seems inherent to gastric segment when compared to ileum/colon.

43.2.4 Complications

Stomach incorporation into the urinary tract is not without its complications, even though the spectrum is somewhat different from an ileo/colocystoplasty. When compared to an enterocystoplasty, the incidence of bacteriuria, mucus production and bladder stones are significantly lower following a gastrocystoplasty. This may be attributed to bactericidal effects of aciduria, decreased mucus and the potential for self voiding thus eliminating need for intermittent catheterization [38, 47]. The risk of spontaneous bladder perforation is also lower, especially when compared to a colocystoplasty [48].

43.2.4.1 Metabolic Abnormalities

While the secretion of acid and chloride is in general a boon for patients with reduced renal function and systemic acidosis, in some cases of gastrocystoplasty, a hypochloremic, hypokalemic metabolic alkalosis can result from overabundant losses or as a result of additional losses via vomiting/gastrointestinal tract. Gosalbez et al. in their study of 34 children who had undergone gastrocystoplasty/continent diversion with stomach observed severe metabolic alkalosis in two patients who presented with seizure disorder and altered mental status with respiratory depression [49].

43.2.4.2 Hematuria-Dysuria Syndrome

This is a complication unique to scenarios where stomach has been used for bladder reconstruction. The symptoms may include suprapubic, penile or periurethral pain, hematuria, dysuria without infection, skin excoriation etc. Two large series of cases undergoing gastrocystoplasty reported an overall 27% and 36% incidence of hematuria dysuria syndrome, respectively [50, 51]. It is more likely to affect patients with a sensate urethra and those who have continued incontinence. While the exact etiopathogenesis is unknown, most of these patients can be treated with H_2 receptor blocker and/or proton pump inhibitors.

43.2.4.3 Malignant Transformation

The traditional understanding was that the risk of malignancy in the augmented bladder was lower in cases of gastrocystoplasty when compared to enterocystoplasty. This was attributed to a lower rate of infections, bacteriuria, nitrosamine formation, bladder calculi etc. in the gastric augment, all of whom are thought to be risk factors for development of malignancy. However, two recent long term follow up studies have shown a much higher risk of malignancy (14.3–27.3%), with gastrocystoplasty than what was thought previously [52, 53].

Peptic ulceration in the augment, hypergastrinemia and sequele of partial gastrectomy are some other complications unique to gastrocystoplasty.

To conclude, use of stomach for bladder augmentation has some clear advantages including a rich and reliable blood supply, thick wall that accommodates ureters in submucosal tunnel, acidific urine, low mucus production etc. It is the only gastrointestinal segment suitable in patients with significantly reduced renal function or in those where no other bowel is available. However, recent reports of an unacceptable risk of malignancy have dimmed the enthusiasm around gastrocystoplasty.

43.3 Ureteral Re-Implantation and Ureteroplasty During Augmentation Cystoplasty

Limin Liao

Augmentation cystoplasty (AC) is generally accepted as a reconstruction procedure in patients with a refractory dysfunctional bladder disorder [54]. AC remains controversial whether or not ureteral re-implantation (UR) is necessary with AC. Some authors believe that concomitant UR is not necessary [54, 55], while others agree that UR should be performed in combination with AC [56–61]. Few studies have addressed whether or not UR should be performed in patients with hydronephroses and ureteral dilation, but without vesicoureteral reflux (VUR) [60, 61]. We have performed anti-reflux procedures with or without ureteroplasties together with AC over the past 11 years [62].

43.3.1 Indications

At our center, the indications for AC are as follows [60–62]: (1) high bladder storage pressure (>40 cm H_2O) or decreased bladder capacity ([BC] < 10 mL/cm H_2O) with or without upper urinary tract (UUT) dilation/deterioration; (2) socially unacceptable urinary incontinence (UI) due to detrusor overactivity (DO) or decreased BC; (3) high-grade and/or low-pressure VUR with UUT deterioration [63]; (4) infectious and inflammatory disorders, such as tuberculous bladder contractures; and (5) serum creatinine (Scr) level significantly decreased after indwelling urethral catheterization (IDUC) in patients with chronic renal failure (CFR), which is defined as a Scr level >1.5 mg/dL (132.6 μmol/L).

The indications for UR during AC are as follows [60, 62–65]: (1) VUR ≥ grade III during storage (Fig. 43.9); (2) VUR starting at low pressures (<10 cm H_2O; Fig. 43.10); and (3) UUT dilation (UUTD) ≥ grade III and/or ureterovesical junction stenosis (UVJS; Fig. 43.11).

The indications for ureteroplasty (ureterolysis and tailoring/shortening) during AC and UR include megaureter, severe tortuous ureter, and constricting ureteric stenosis (Fig. 43.12).

43.3.2 Surgical Technique

AC was performed with different detubularized segments of bowel, including the sigmoid, ileum, and ileocecum. A concomitant anti-reflux procedure with construction of a hemi-Kock nipple valve in the native bladder or in the bowel wall was performed. The nipple valves were first stapled on the ureteral serosa for fixation, then the ureteral nipple valve and bladder or bowel were sewed mucosa-to-mucosa. The ureteric units with megaureter, severe tortuous ureter, and constricting ureteric stenosis (Fig. 43.12) were performed with simultaneous ureteroplasties, including ureterolysis and tailoring/shortening. Ureterolysis refers to mobilization and straightening of the ureter. Tailoring refers to shortening the length of the ureter, and reducing the diameter of the megaureters. Whether or not UR would be performed in native bladder or bowel based on the friability of the mucosa, severity of contracture of the native bladder, and bladder wall thickness was determined. The Mitrofanoff procedure was performed in patients with urethral strictures, serious spasm of the urethral sphincter, and urinary incontinence (UI). An appendix-umbilical stoma was used for intermittent catheterization (IC).

The suprapubic catheter was removed 3 weeks postoperatively, and a ureteral catheter was removed within 4 weeks before video-urodynamics (VUD). The patients were trained to perform IC 4–5 times per day. The volume of IC was referred to as the maximum bladder capacity (MBC) from VUD. Anti-muscarinics were used if VUD indicated DO and a small MBC.

43.3.3 Therapeutic Effects and Experience

A retrospective study from 173 patients at our center showed that AC in combination with UR is relatively safe and effective for refractory dysfunctional bladder and relevant UUT deterioration based on the following findings: (1) significantly decreased $P_{det.max}$ and increased MBC and BC; (2) improved UUT dilation and renal function; and (3) acceptable complications [62].

Based on the literature, the colon is always the second choice for AC [66], but the sigmoid bowel has been the first choice at our center because of the thick muscular wall, large

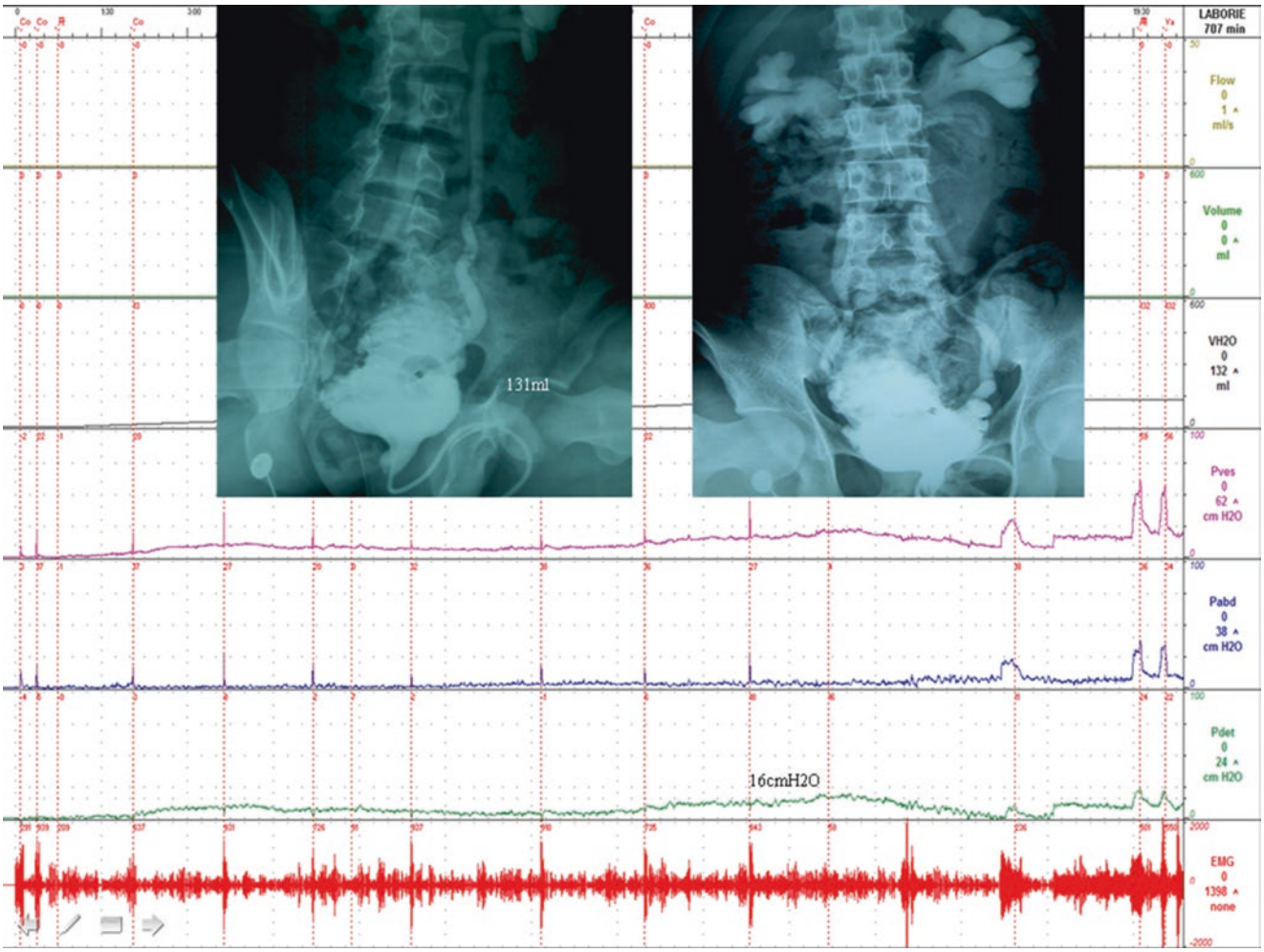

Fig. 43.9 Video-urodynamics for a male with myelomeningocele (19 years of age): bilateral VUR with grade IV occurred during storage at a volume of 90 mL and P_{det} of 16 cm H_2O

lumen, abundant mesentery, and maneuverability. Skinner et al. [67] reported that urinary diversion should not be offered to patients with abnormalities in renal function; however, for these patients, AC may stabilize renal function [68]. We prefer IDUC for the pre-operative preparation and evaluation. If the Scr gradually decreases, the Scr is more likely to indicate recovery of renal function post-operatively; however, those patients with ureterovesical junction stenosis (UVJS)/ureterovesical junction obstruction (UVJO) or severe ureteric adhesions usually do not exhibit improvement in the Scr level by IDUC. We found that the pre-operative glomerular filtration rate (GFR) has a negative association with the post-operative Scr level, thus the GFR is one of the predictive factors. Those patients in whom renal function deteriorated after surgery had a high Scr level, a low GFR, severe atrophy of the kidney, and renal anemia and/or renal hypertension pre-operatively, although the Scr level significantly decreased through pre-operative drainage. The serial urodynamic and final Scr data were keys in supporting the surgical management in this group of high-risk patients.

Most of our patients underwent AC combined with UR. The patients were relatively unique and unusual in that there was a relatively high proportion of adults with congenital neuropathic bladder without correct bladder management. VUD and MRU demonstrated that most of these patients had high-grade VUR, UVJS/UVJO, ureteral tortuosity and adhesions, and severe UUTD.

There are controversial views regarding the management of refractory dysfunctional bladder disorders [7, 54–56, 69]. VUR can be eliminated with AC alone; however, a high incidence of residual VUR is associated with febrile UTI and UUT scarring. Of note, AC alone did not protect renal

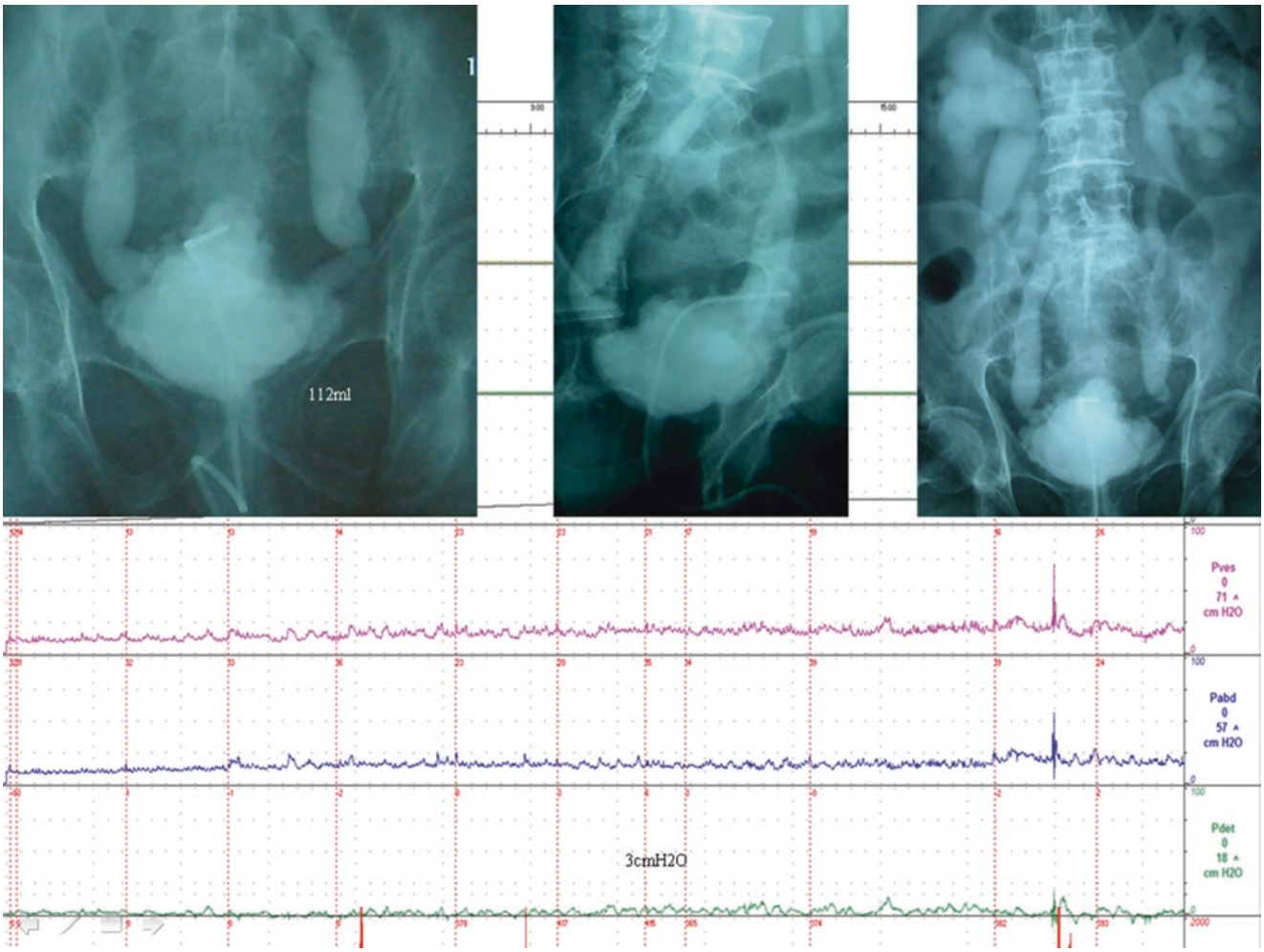

Fig. 43.10 Video-urodynamics for a male with a myelomeningocele (34 years of age): bilateral VUR with grade V occurred during storage at a volume of 80 mL and P_{det} of 3 cm H_2O

function, and UR with ureteric tailoring/shortening is recommended. Based on our experience, patients with low-pressure VUR, high-grade VUR, high-grade VUR combined with UVJS, or ureteric tortuosity and adhesions, UR should be performed (Figs. 43.12, 43.13, and 43.14).

The reasons for post-operative VUR after UR may be related to insufficiently increased BC and DO in the early stage, which develops due to edema and inflammation of the bladder or bowel wall. Post-operative VUR can be well-controlled with anti-muscarinics, or natural improvement of BC due to the neo-bladder becoming soft and flexible.

UVJO/UVJS may be related to VUR, ischemia, chronic inflammation, fibrosis, and thickening of the bladder wall. UVJO usually leads to hydronephrosis, ureteric dilatation, tortuosity, adhesions, and chronic renal failure (CFR). The sites of obstruction usually begin at the UVJS, and fibrotic cords always form at tortuous points. UR with ureteric adhesiolysis and tailoring/shortening are necessary in the UVJO/UVJS. Hydronephrosis in the absence of VUR and UVJO results from ureter tortuosity and adhesions above the bladder wall; for these patients, IDUC or AC does not improve UUT deterioration, and UR with ureterolysis and ureteric tailoring/shortening are usually combined with AC (Figs. 43.12 and 43.13).

Vesicoureteral anastomosis stenosis (VUAS) is related to the following factors: (1) the ureter and bladder wall are very thick and stiffness due to scarring and fibrosis with a poor blood supply (Fig. 43.15); (2) the ureter, after ureterolysis, straightening, and shortening, had a poor blood supply; and (3) chronic inflammation in the bladder and ureter. In our clinical practice, we strive to minimize the risk of VUAS, as follows (Fig. 43.16): (1) ureteral blood supply must be protected during ureterolysis, mobilization, and tailoring/shortening; (2) if the ureteral length is sufficient, the scarred and fibrotic part of the ureter must be removed; (3) the ureter is completely flipped over to form a 1-cm nipple valve, then the nipple valve and bladder or bowel are sutured with four needles mucosa-to-mucosa and 1–2 needles serosa-to-serosa

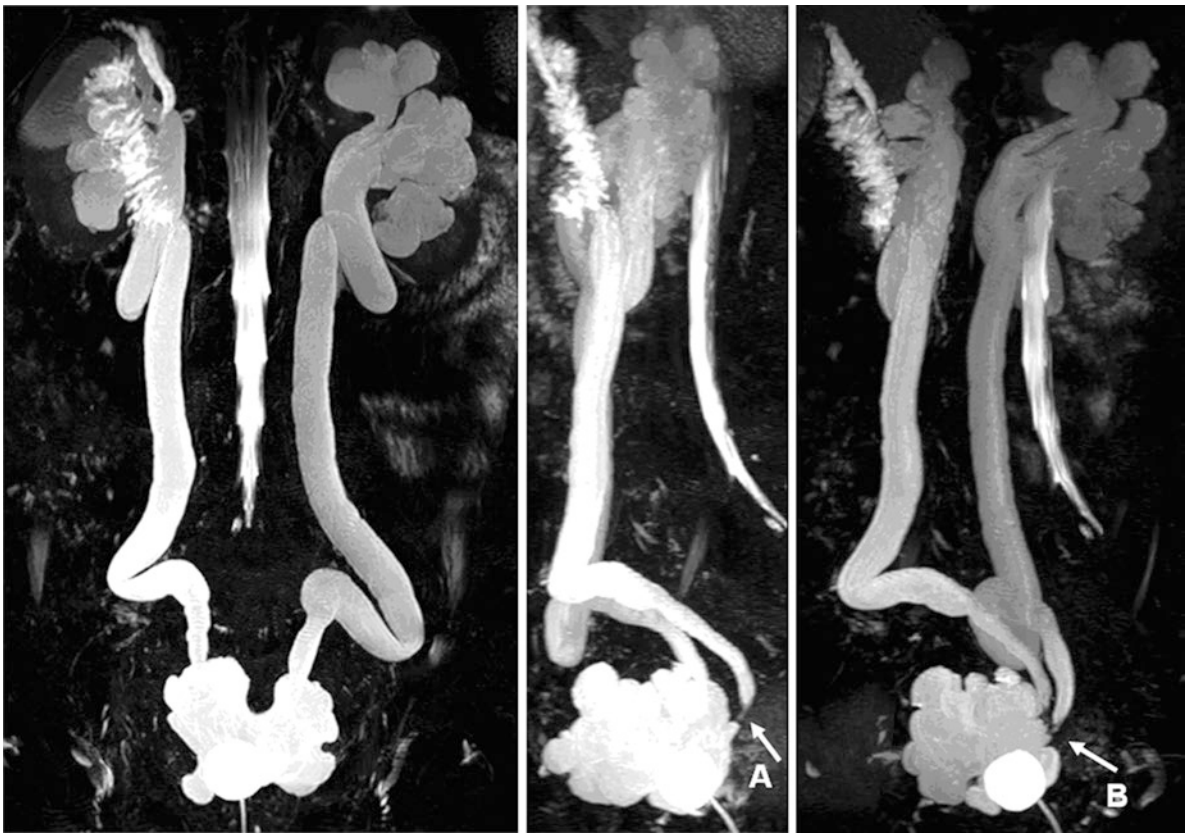

Fig. 43.11 Magnetic resonance urography (MRU) for a male with myelomeningocele (33 years of age): MRU-UUTD grade IV and ureterovesical junction stenosis (**A**: right, **B**: left)

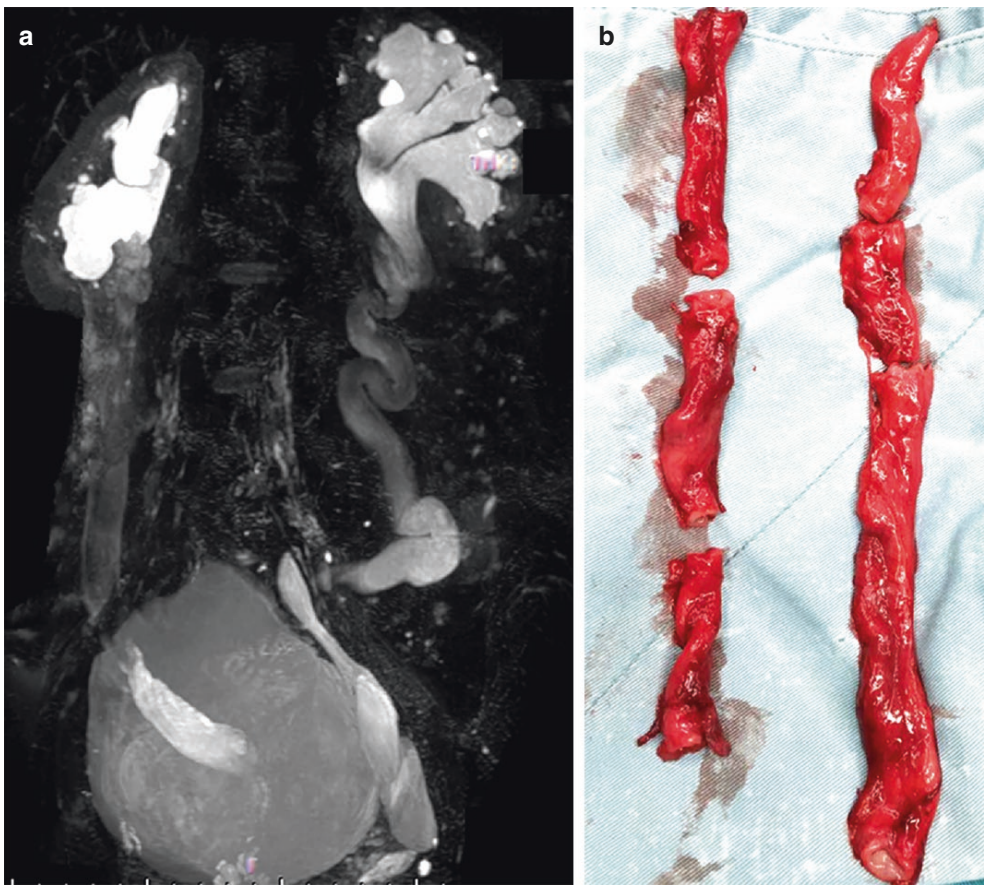

Fig. 43.12 A male with myelomeningocele (23 years of age): (**a**) MRU-UUTD grade was IV pre-operatively. Both sides showed hydronephrosis, ureteric dilatation, and severe tortuosity. (**b**) Ureteral re-implantation (UR) with ureteric adhesiolysis and tailoring/shortening was performed during AC, and both ureters were removed at approximately 20 cm

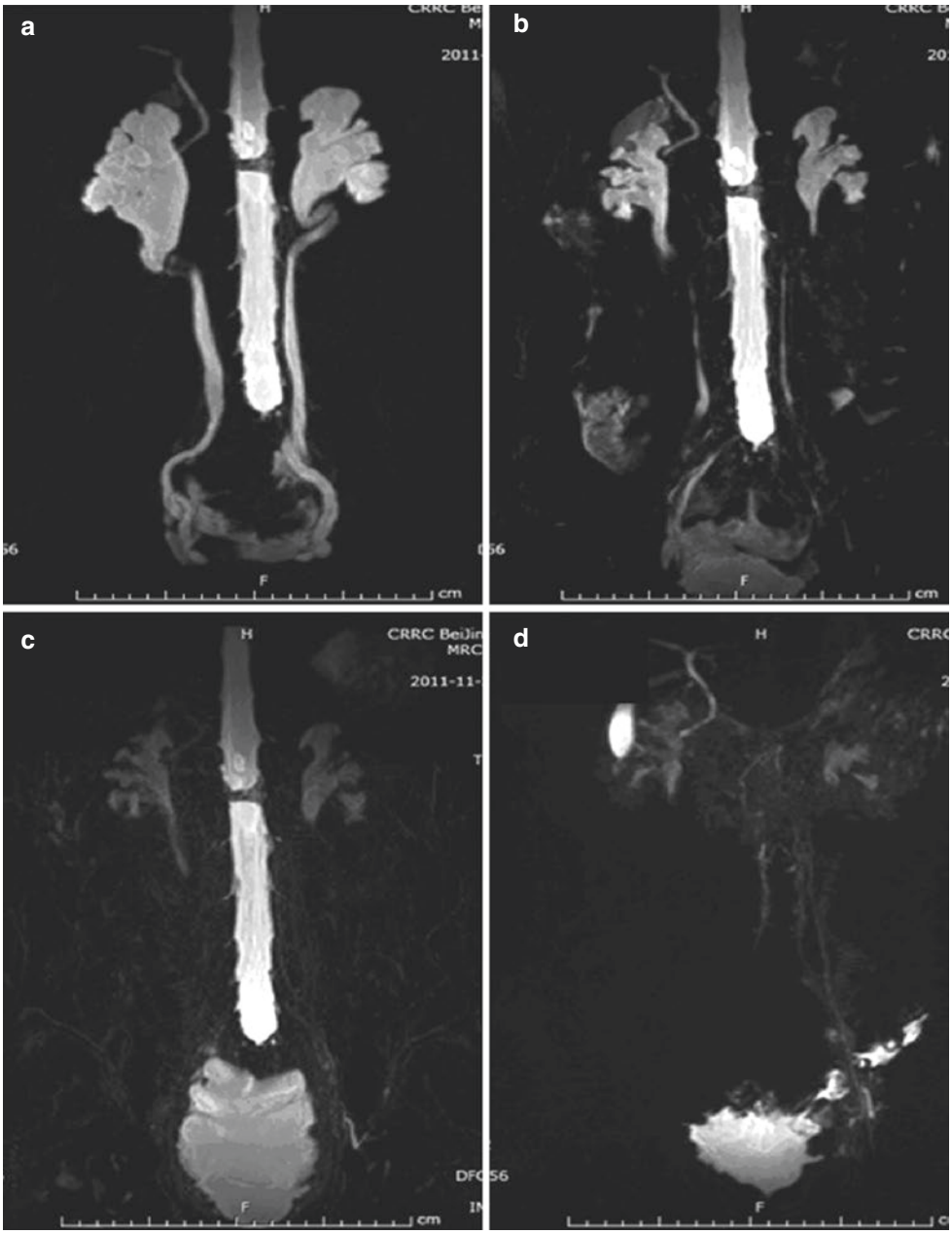

Fig. 43.13 Magnetic resonance urography (MRU) follow-up of AC combined with UR for a male with myelomeningocele (27 years of age): (**a**) MRU-UUTD grade IV pre-operatively. (**b**) MRU-UUTD grade II 3 months post-operatively. (**c**) MRU-UUTD grade I 1 year post-operatively. (**d**) MRU-UUTD grade 0 4 years post-operatively

with 5-0 absorbable suture; (4) if the bladder wall is thickened due to scarring and fibrosis, the bowel wall is chosen; (5) in the bladder or bowel wall, a submucosal tunnel is avoided and a hole should be sufficiently large for the size of the ureter; and (6) an indwelling double "J" stent (7- or 8-Fr) is kept for at least 4 weeks.

A successful nipple valve with anti-refluxing function in the bladder is shown by cystoscopy after 1 year of surgery (Fig. 43.17).

AC with UR may have the other complications or problems. In the early stages post-operatively, urinary incontinence (UI) is usually attributed to sphincter weakness, DO, and lower bladder compliance. The anti-muscarinics are usually used to inhibit DO in neobladders, and UI may be improved significantly. AC with the ileum is more susceptible to bowel obstruction, but this complication differed from our patient experience. Troublesome diarrhea occurred in patients who underwent ileocystoplasties, which may be related to the loss of large segments of terminal ileum [70]. Asymptomatic bacteriuria in patients on IC is common [71]. Risk factors predisposing to UTI include mucus accumulation and stasis. With respect to prophylaxis for UTI, the patients were asked to irrigate their bladders regularly with saline with or without iodophor to clear mucus and reduce

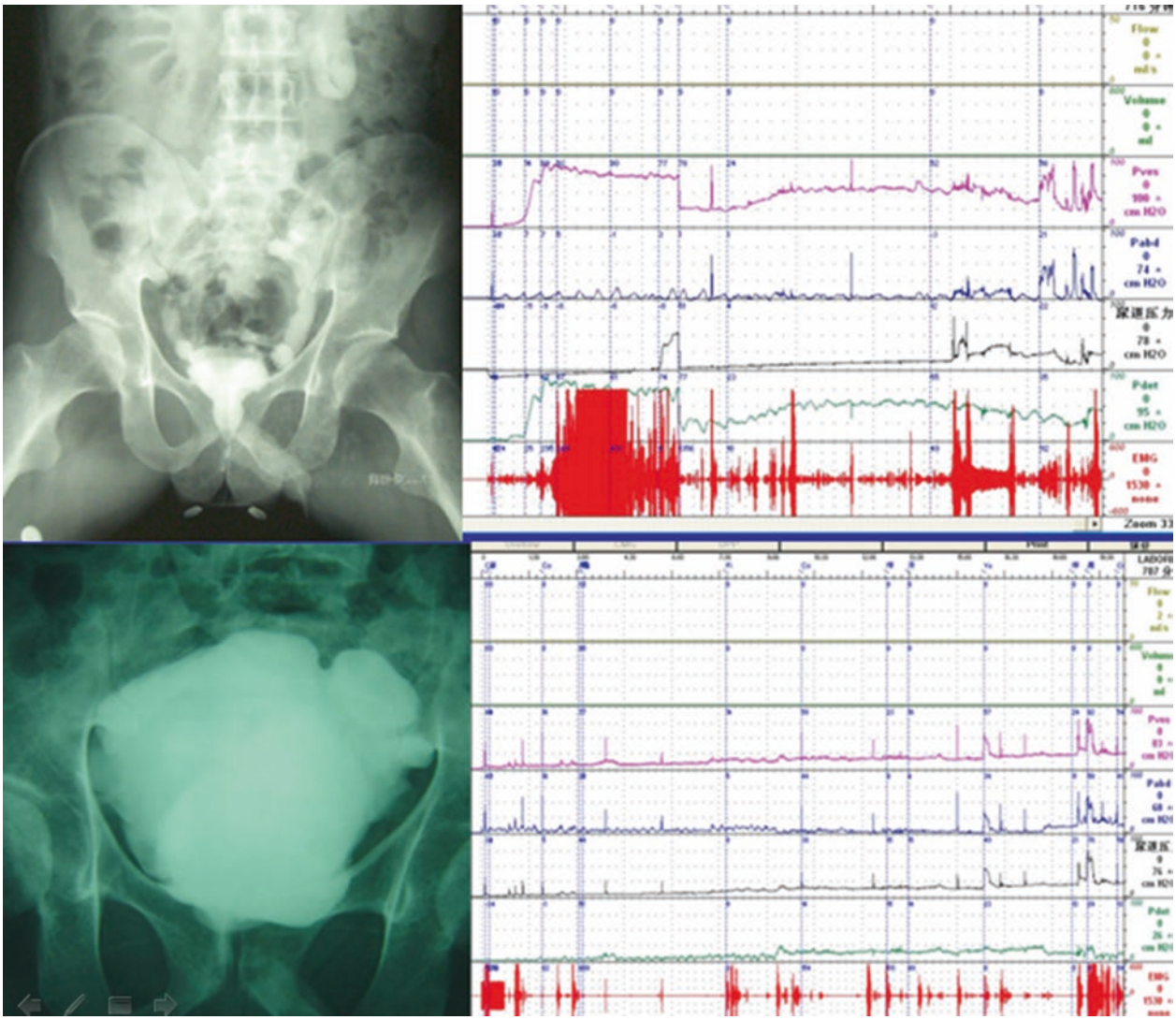

Fig. 43.14 Video-urodynamics follow-up of AC combined with UR for a male with myelomeningocele (30 years of age): Upper. VUR grade V, detrusor overactivity (DO) and reduced bladder capacity pre-operatively. Lower. VUR and DO resolved, and bladder capacity increased from 27 to 450 mL post-operatively

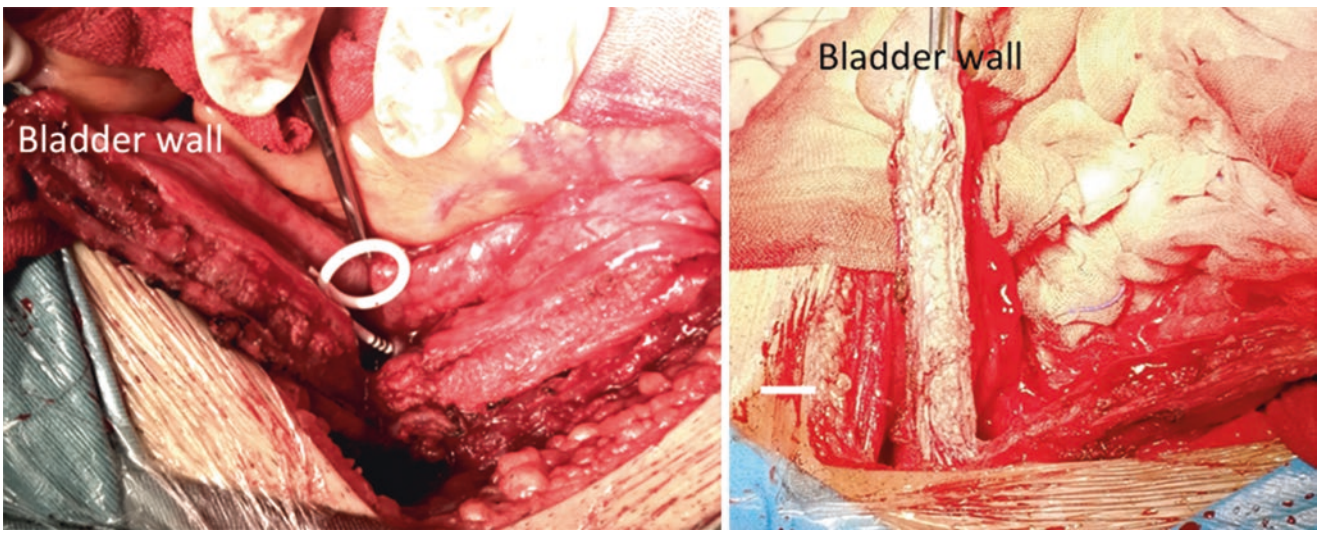

Fig. 43.15 Bladder wall thickened and stiff due to scarring, fibrosis, and poor blood supply in two patients with neurogenic bladder

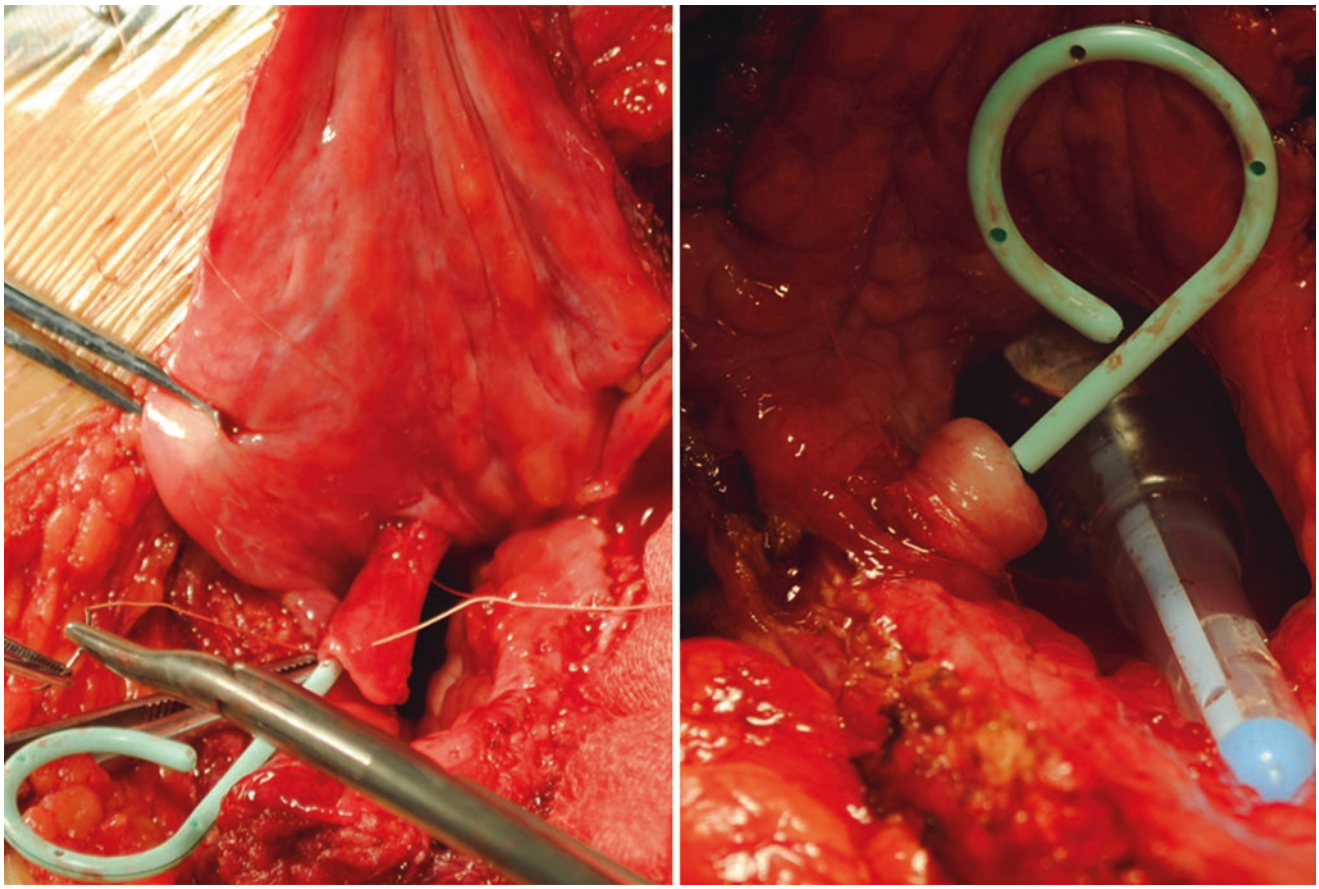

Fig. 43.16 Augmentation cystoplasty with anti-refluxing ureteral re-implantation

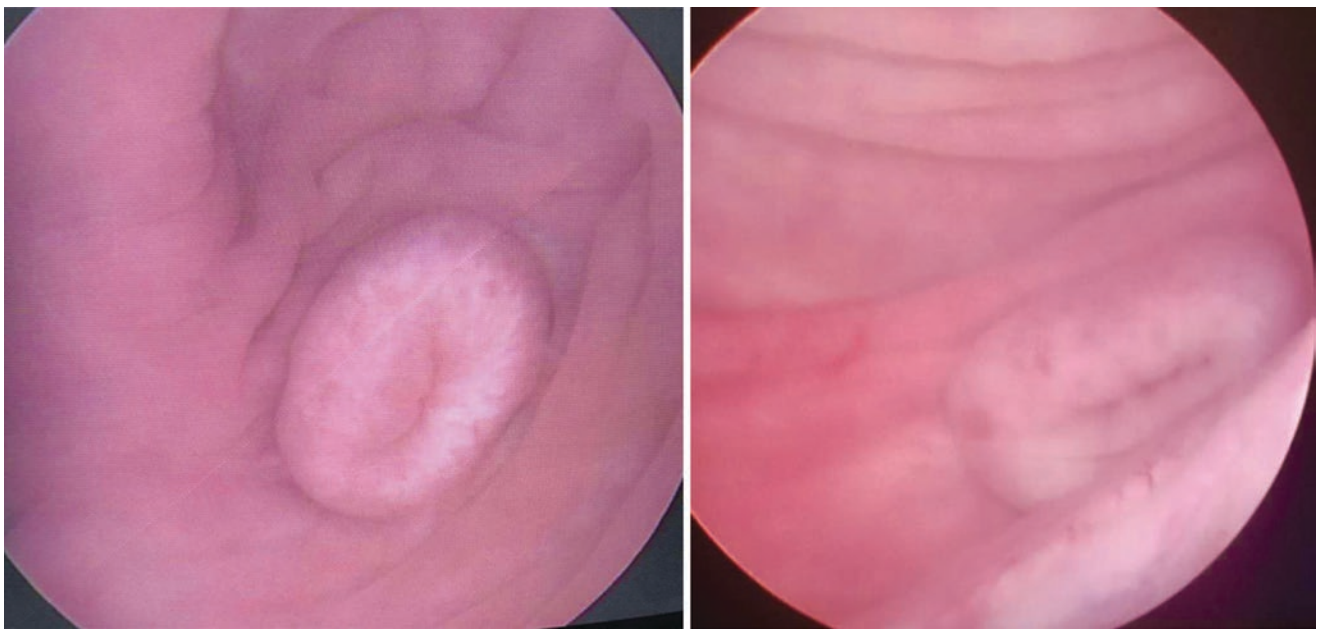

Fig. 43.17 The successful anti-refluxing nipple valves in the bladder shown by cystoscopy after 1 year of augmentation cystoplasty with anti-refluxing ureteral re-implantation

the breeding of harmful bacteria. The etiology of stones after AC includes incomplete emptying, excessive mucus production, metabolic abnormalities, and chronic bacteriuria [72]. Prevention strategies include increased fluid intake, appropriate IC, regular bladder irrigation, and prompt treatment of UTIs [73]. A study demonstrated well-compensated acidosis following incorporation of the ileum into the urinary tract [74]. It is difficult to discern the etiology of this undesired outcome, and it appeared to be dependent on renal function before surgery. Although the incidence was low in our patients, more cases could possibly develop acidosis with longer follow-up.

43.4 Conclusions

Our experience showed that concomitant UR with AC may be beneficial for patients with low-pressure or high-grade VUR, UVJO/UVJS, or ureteral tortuosity and adhesions, and/or severe UUTD, especially for those patients with a long medical history. The indications for AC and/or UR are worthy of additional investigation.

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Ureterocystoplasty

44

Limin Liao

44.1 Advantages and Disadvantages

Ureterocystoplasty (UCP) was first reported in 1973 and became popularized in the early 1990s [1–3]. Since the 1990s, not only have the indications for UCP changed, but also the technique has been modified. The surgery involves incorporating a strip of dilated ureter into the bladder, providing a urothelium-lined augmented segment with muscular backing and good elasticity. As a result, the complications inherent in enterocystoplasty (ECP) are avoided. Although most published papers describing this technique have reported encouraging results, the number of patients enrolled was often in the single digits [4, 5]. In this chapter, we review what is known about UCP.

An ideal tissue for increasing bladder capacity and improving bladder compliance should have transitional epithelium that is relatively impermeable and will avoid the metabolic changes [6]. A segment of the small or large bowel has been used for bladder augmentation conventionally. The presence of gastrointestinal mucosa in the urinary tract leads to the complications, including excessive mucus production, urolithiasis, urinary tract infection (UTI), malignancy, metabolic disorders and fistula formation [7]. Bladder autoaugmentation results in capacities that are potentially decreased compared with other procedures [8].

Dilated ureteral tissue is an excellent source for bladder augmentation. Ureteral tissue is lined by transitional cell epithelium and backed with muscle. The main benefits of ureteral bladder augmentation are associated with the absence of mucus production, the decreased possibility of UTI and stone formation, and no spontaneous perforation [9]. Ureteral bladder augmentation also avoids the metabolic disturbances secondary to the absorption of urine by the intestinal mucosa and the increased frequency of urinary and gastrointestinal complications [10, 11].

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Although the ureter is the best choice currently available for bladder augmentation, UCP cannot be performed frequently as it requires transureteroureterostomy or nephrectomy of a non-functioning unit as a prerequisite [12]. Moreover, UCP has limitations, such as difficulty in obtaining sufficient ureteral tissue for augmentation, which may result in repeat augmentation [13]. In addition, one drawback of using the ureter in AC is the paucity of patients who have both a megaureter and a non-functioning kidney. It is possible to experimentally dilate a normal ureter and successfully use this tissue for AC in an animal model [14]. Another drawback is the patients might require CIC to completely empty the bladder [15].

44.2 Surgical Technique

Several donor sites have been suggested to provide the needed ureteral tissue for UCP, including non-refluxing megaureters, dilated ureters, refluxing ureters, and distal ureteral segments [16–18]. Previously, UCP had been used only at the time of concurrent nephrectomy because it was thought that an adequate bladder volume can be achieved only by the use of the renal pelvis and the megaureter or most of the megaureter (Figs. 44.1 and 44.2) [19].

Recent studies have shown that the lower two-thirds of a dilated ureter can provide the desired bladder capacity, so that the ipsilateral kidney can be preserved by forming a transureteroureterostomy [20]. Both ureters can be used, with one to enlarge the bladder and the other to replant into and to form a continent diversion stoma in the bladder using the lower ureter for augmentation [21].

Perovic et al. [22] also performed a variant of UCP with preservation of the kidney by using the distal ureter for bladder augmentation and the proximal ureter for re-implantation into the bladder. Babu et al. [23] attempted a similar technique with Mitrofanoff in a patient. Tandem UCP [21] and tea-pot UCP [24] are similar techniques preserving ureter bladder continuity and the vascularity. Ramalingam et al.

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_44

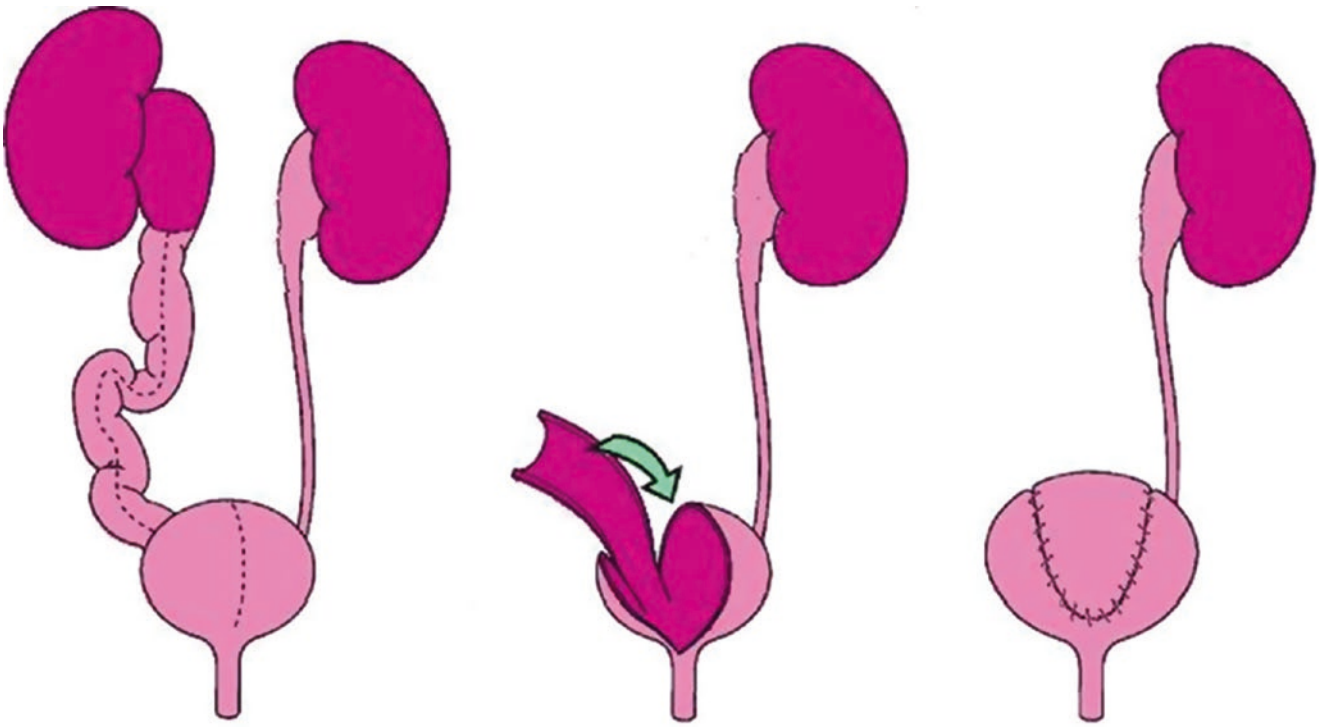

Fig. 44.1 The RCP involves incorporating a strip of dilated ureter into the bladder and concurrent nephrectomy

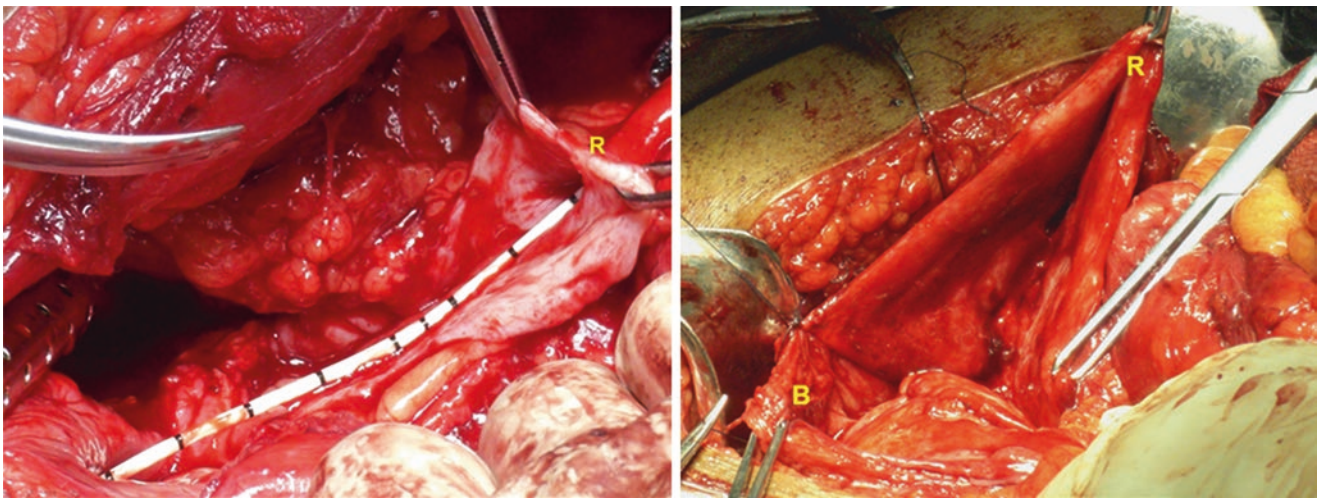

Fig. 44.2 The RCP procedure. Left: a strip of dilated ureter. Right: incorporation of a strip of dilated ureter into the bladder. *R* ureter, *B* bladder

[25] thought that laparoscopic UCP is a viable option, especially for the patient who has had multiple open surgeries and is awaiting further open surgery.

44.3 Indications and Therapeutic Effects

The indications for UCP include a variety of bladder dysfunctions, i.e., low bladder capacity, poor compliance, and raised intravesical pressure. The causes may be NB, posterior urethral obstruction, bladder exstrophy, and ureteric duplication with reflux, all of which are frequently associated with poor renal function and massively dilated, refluxing ureters [26, 27].

UCP is indicated in NB patients in whom conservative therapy has failed. Several studies have determined the parameters to predict the long-term success of UCP in NB. Zubieta et al. [28] reported no re-augmentation after 16 months of follow-up in 32 patients, of whom 20 had a NB, and suggested that UCP is an excellent choice for

increasing bladder capacity and improving compliance. Husmann et al. [13] reported that UCP has little-to-no merit in patients with NB, and UCP is best considered in the presence of a non-refluxing megaureter >1.5 cm in width or in the presence of mild bladder non-compliance (≥20 mL/cm H_2O); however, according to Ramalingam et al. [25] there was an improvement of compliance and capacity in spite of reflux. Kajbafzadeh et al. [24] treated 13 children with end-stage NB and refluxing megaureters with simultaneous tea-pot UCP and Mitrofanoff appendicovesicostomy. At the end of the follow-up period, all patients were dry with CIC and/or voiding. The median post-operative bladder capacity was increased significantly compared to the pre-operative evaluation. During follow-up, bladder compliance and the serum creatinine level were improved significantly.

UCP is most commonly described in children with a median age of 4.7–9 years [3, 4, 18], but this technique is not limited to use in children. We reported a case wherein UCP was performed in a 28-year male who presented with a small capacity NB, a grossly dilated and tortuous left ureter, and a non-functioning left kidney. The bladder capacity increased adequately post-operatively and he is doing well at a follow-up of 3 years (Fig. 44.2) [29]. Taghizadeh et al. [15] also demonstrated that UCP works well in adult patients.

For patients with NB, the long-term success is based on a number of important factors. Careful evaluation of abdominal ultrasonography, urodynamic studies, and voiding cystourethrography is essential in selecting the right patients for UCP [12]. When performing UCP, care is taken to preserve the blood supply to all parts of the distal ureter during augmentation. This step is an essential part of the procedure, and safeguards the success of the technique [22]. The bladder must be able to empty completely by CIC.

UCP has gained in popularity as an attractive material for AC. The good candidates are those patients with a large-caliber ureter created by massive reflux or hydroureteronephrosis and an ipsilateral poor renal function [4]; however, UCP has also expanded to the patients with salvageable renal function in which a transureteroureterostomy is performed [17, 22].

When should UCP be performed? There is no clear consensus on the timing of UCP coincident with kidney transplantation [30]. The renal transplantation is usually performed months-to-years after UCP so that immunosuppression does not compromise the healing process and does not increase the risk of complications [1].

44.4 Experience of Treatment

An important step for successful UCP is special attention to preserving the ureteral vascularization. After UCP, urodynamics or video-urodynamics should be performed again to confirm improvement of bladder compliance, especially before considering kidney transplantation [5].

The technique lends itself well to patients with renal failure [3, 4, 18]. A non-functioning kidney is more likely to have a dilated ureter. The advantages of the extraperitoneal approach of UCP can be applied to laparoscopic-assisted UCP and peritoneal dialysis [18]. Functioning kidneys are not a contraindication to UCP [28].

Although it is possible to use a re-implanted ureter for UCP, the ureter could be insufficiently vascularized to undergo UCP, which would result in the high failure rate [19]. UCP has been confined to patients who already have a dilated ureter; however, the possibility of UCP by balloon dilating a normal-caliber ureter in animals was explored [31].

44.5 Conclusions

In conclusion, although the procedure is safe and effective, UCP is not a panacea and has strict indications. Larger studies with longer follow-up are needed for the long-term outcomes of UCP.

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Tissue-Engineering Bladder Augmentation

45

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45.1 Introduction

Tissue engineering (TE) and regenerative medicine combine cells and biomaterial techniques to encourage regeneration of new, healthy tissues and offer an alternative approach for the replacement of deficient organs. Currently, TE techniques have been developed to generate prostheses for different urologic tissues and organs [1]. The lower urinary tract (LUT) is responsible for urine storage and its evacuation. The urinary bladder and urethra consist of epithelium on the lumen surrounded by a collagen-rich connective tissue and muscle layer. Many pathologies affect the LUT and demand their replacement, and hence the health and quality of life of the patients at different ages and genders.

The main necessities for bladder surgical reconstruction are vesical exstrophy, neurogenic bladders, contracted bladder, and urothelial carcinoma. The gold standard technique for bladder replacement is the use of intestinal segments. Because the intestine is structurally and functionally different from the urinary bladder, many complications exist, such as hypocontractility, hematuria, dysuria, urolithiasis, neoplasia, ectopic mucus production, and metabolic imbalances due to urine absorption by the intestinal mucosa. Various urethral conditions, such as inflammatory and post-traumatic strictures, congenital defects, often require urethral reconstruction [2–6]. Currently, urethral conditions are treated with autologous grafts or flaps from genital skin or the buccal mucosa. There may be a limited donor supply of tissues needed for long segment replacement. Despite how good the initial result is, in the long term, all skin tubes (from genital or extragenital sources, whether used as grafts or flaps) have a tendency to deteriorate. For this reason, TE and regenerative medicine have evolved to compensate for the replacement of these organs to prevent complications and improve the quality of life for patients with major diseases necessitating bladder and urethral substitution.

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45.2 Cell Sources for Tissue Engineering of LUT

The ideal strategies for tissue engineering of LUT would be tissue-specific autologous cells harvested from an individual, cultured *ex vivo* to be expanded, and re-introduced into a second site for repair. Because urinary tract organs are composed of two cell types, a challenge would be to obtain differentiated smooth muscle and urothelial cells from progenitors or stem cells [7].

45.2.1 Progenitor Cells

These cells reside within each organ, have limited self-renewal capacity, and differentiate into only one defined cell type.

45.2.1.1 Epithelial Cells

(1) Autologous urothelial cells (UCs): classically, these cells are obtained from urinary bladder and have often been used in urethral and bladder reconstruction. (2) Autologous epidermal cells: these cells can be harvested from penile foreskin because of the abundant resources. (3) Autologous oral keratinocytes have also been used as a source of epithelial cells.

45.2.1.2 Smooth Muscle Cells (SMCs)

Autologous SMCs offer the potential for improved extracellular matrix (ECM) compliance and tissue elasticity, in addition to angiogenesis and epithelial maturation. In the bladder, SMCs are essential to allow for contraction of the engineered tissue for urine expulsion.

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_45

45.2.2 Stem Cells

Stem cells are undifferentiated cells that have self-renewal potential. *In vitro* studies have shown that human fat-derived mesenchymal stem cells (MSC) can increase smooth muscle gene expression. The combination of stimulation by humoral factors and co-culture with primary urothelial cells caused an increase of smooth muscle-specific gene expression in the treated MSCs. Bone marrow stem cells (BMSCs) can be differentiated into SMCs and UCs. Adipose-derived stem cells (ADSCs) have been successfully differentiated into UCs with all-trans-retinoic acid or co-culture with UCs [8].

45.3 Scaffolds for Tissue Engineering of LUT

The ideal biomaterial for bladder and urethral regeneration should have constant attachment of mature epithelial cell layer on the luminal surface and harbor multiple cell layers of SMCs on the outside, and should also provide adequate mechanical support and prevent collapse prematurely. The biomaterial scaffolds facilitate the delivery of cells to desired sites in the body, define the three-dimensional space for the formation of new tissues, and provide mechanical support for the regenerated tissues. Three different classes of biomaterials are used, as follows: naturally-derived materials, acellular tissue matrices and synthetic polymers. The self-assembly technique is an alternative method for tissue engineering [9].

45.3.1 Synthetic Polymers

Synthetic polymers, such as polyglycolic acid (PGA) and polylactic acid-co-glycolic acid (PLGA) are made of macromolecules assembled with covalent links. The advantage is the capacity to manufacture any form of an organ in three dimensions, quantitatively and reproducibly, and at a relatively low cost.

45.3.2 Acellular Tissue Matrices

Acellular tissue matrices are decellularized tissues, such as small intestinal submucosa (SIS) and bladder acellular matrix (BAM). They have the advantage of providing inherent bioactivity and mechanical similarity to native ECM due to the inherited presence of growth factors and ECM proteins.

45.3.3 Self-Assembled Engineered Tissue

The self-assembly method is able to produce a tissue built by the cells in which a dense ECM is completely produced by fibroblasts. The absence of an immunologic response should reduce the inflammatory and fibrotic reactions. Cells can receive the correct signaling for appropriate differentiation. Then, the transplanted engineered tissue is very similar to the tissue that has to be replaced.

Naturally-derived materials and decellularized tissue matrices have biological properties that better mimic native tissue or organ extracellular matrix, but these are limited in supply. In contrast, synthetic scaffolds can be produced on a large scale. The self-assembly technique proves to be useful for tissue reconstructions, ranging from skin-to-blood vessels [10].

45.4 Tissue Engineering of the Urothelium

TE of the urothelium can play a key role in reconstructive urology. Recently, graft tissues appear to have an advantage over matrices. These therapies depend on cell isolation and propagation *in vitro*. The choice of the correct cell source is crucial. The buccal mucosa was the most adequate substitute in urethral reconstruction [11]. TE has the potential to improve the quality of repair by identifying a new source of urothelium through the seeding of stem cells on an acellular tissue or scaffolds [7, 12, 13]. A functional multilayer urothelial sheath was recently cultivated from bladder wash-separated urothelium cells [14, 15].

45.5 Tissue Engineering of the Urinary Bladder

The generation of a bladder wall requires a multilayer cellular scaffold, and vascularization and innervation of the united smooth muscle structure. The addition of growth factors might enhance the regeneration of an acellular matrix [16].

A non-seeded scaffold technology can theoretically be the ideal strategy for bladder replacement because non-seeded scaffold technology is simple and does not require cell harvesting and *in vitro* culture. These scaffolds were thought to enhance tissue regeneration and recruit the local and systemic stem cells to the site of implantation to contribute to new tissue formation. When implanted, these scaffolds should imitate the natural ECM to orchestrate the different steps involved in the regeneration process, which is why naturally-derived ECM matrices were the first to be used for this approach. SIS and BAM were widely explored in experimental studies. For a long time now, it has been reported that acellular matrices are able to sustain proliferation of the urothelium and SMCs arising from adjacent normal tissue together with the blood vessel and nerve regeneration. Current developments in building BAM scaffolds facilitate the interactions between the matrix and surrounding tissue cells to allow the output of cell-seeded grafts used as the bladder replacement material.

SIS-based bladder tissue regenerative medicine allows the whole reconstruction of three normal bladder like-layers together with the vascular network [17, 18]; however, non-seeded scaffolds failed to show full regeneration of the bladder wall. Approximately 30% of the smooth muscle layer is able to grow back. The failure of cell-free scaffolds to replace bladder can be attributed to many factors, including extensive scarring within the graft due to xenographic or non-autologous nature of the graft and early exposure of the scaffold to urine, which induces scarring. Urine is toxic to the recruited progenitor and stem cells. Additionally, the lack of a muscle cell layer decreases the elasticity of the wall and prevents bladder contraction and cycling.

Atala et al. [19] reported a clinical trial of TE bladders. Bioartificial organs were created with autologous bladder cells seeded onto collagen-polyglycolic acid scaffolds and transplanted with an omental wrap in patients. The TE bladders displayed a physiologic tri-layered morphology and clinical parameters were stable over a 5-year period. The use of adult organ-specific cells has limitations, such as difficulty in harvesting, low proliferative capacity, and reduced functional quality. Seeding of scaffolds with stem cells might help to generate a bladder wall [20]. Synthetic polymers for cell-seeded 3D scaffold-based bladder tissue engineering, in addition to being endowed with essential biocompatibility properties, non-phlogogenic without inducing foreign-body tissue reactions, non-immunogenic, and non-cancerogenic must be able to adequately support seeded cell kinetic peculiarities, particularly due to interactions of specific soluble growth factors with transmembrane cell integrin receptors.

45.6 Clinical Application of Tissue-Engineering Bladder Augmentation

Bladder augmentation is required for some clinical indications in patients with NB. Due to the limited indications for auto-augmentation and ureterocystoplasty, enterocystoplasty remains the gold standard therapy [4]; however, enterocystoplasty is associated with serious complications. Composite cystoplasty has been proposed to avoid these complications by substituting materials. Our group and others reported promising results of SIS TE cystoplasty [17, 18]. SIS derived from pigs allows multilayered cell growth and urothelial differentiation, supports the growth of human urothelial cells, and is rapidly degraded. Our work showed that SIS caused bladder regeneration in rabbits (Fig. 45.1) [17]. Kropp et al. [21] also evaluated SIS as a possible AC material. Thus, SIS is the potential biodegradable material for clinical use in AC.

In recent years, bladder regeneration has been shown to be feasible using SIS TE techniques. SIS promotes regeneration of a variety of host tissues in clinical application. This

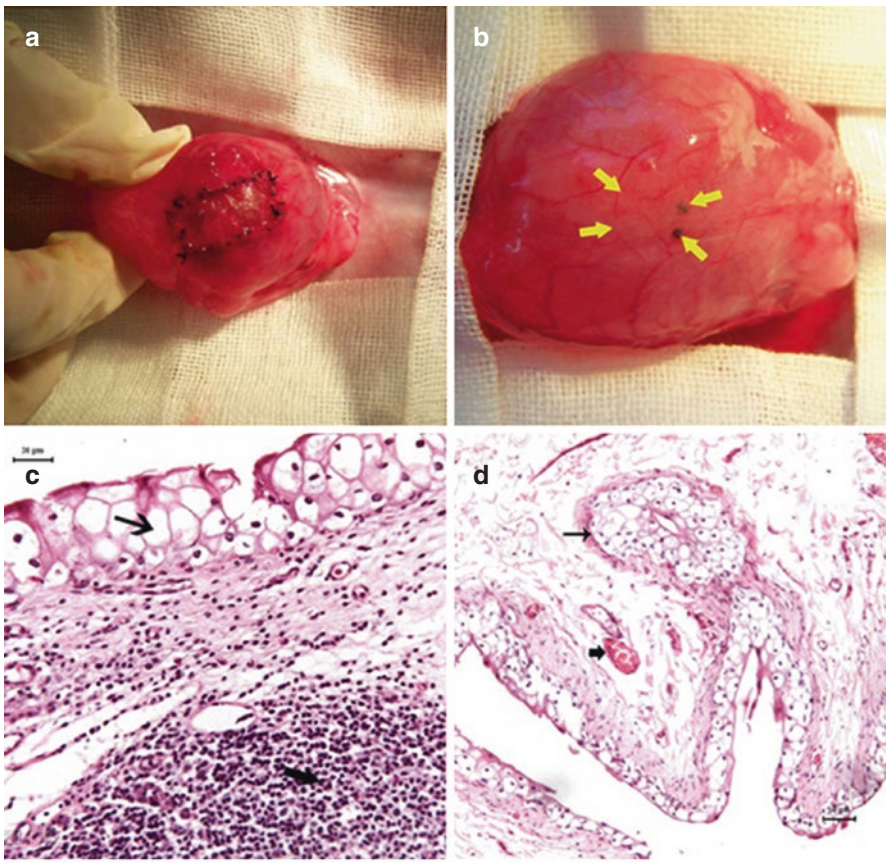

Fig. 45.1 Macroscopic and microscopic (HE) evaluation in the rabbit model. (**a**) The SIS patch (1.0 × 2.0 cm) was grafted onto the host bladder. (**b**) Regenerated tissue in the arrows 24 weeks post-operatively. (**c**) Thin arrow marked the regenerated transitional epithelium in the region of the SIS graft. Coarse arrow marked the infiltrated inflammatory cells (×20). (**d**) Thin arrow marked the regenerated transitional epithelium. Coarse arrow marked the new vessels (×10)

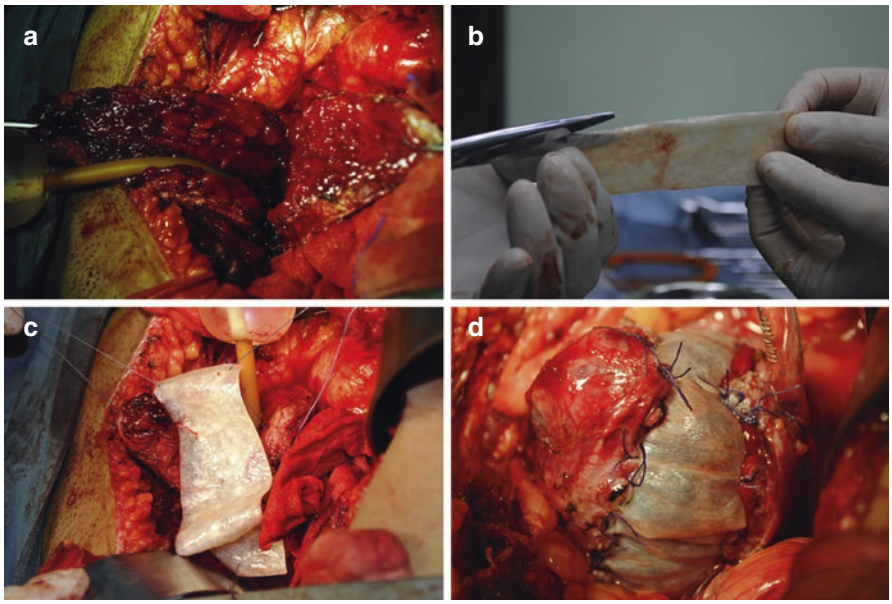

Fig. 45.2 Tissue-engineering bladder augmentation with SIS in a patient with neurogenic bladder. (**a**) Sagittal direction incision of the anterior and lateral walls of the opened bladder. (**b**) SIS scaffold fashioned into a strap shape. (**c**) SIS scaffold anastomosed to native bladder with running 3-0 polyglycolic sutures. (**d**) Cvovering SIS grafted bladder with soft perivesical tissue and omentum flap

characteristic is likely due to the persistence of many elements required for normal cell growth, differentiation, and functioning. We performed TE bladder augmentation with SIS in eight patients (A-H) with neurogenic bladder (Fig. 45.2) [18]. The approval for this study from the ethics committee of China Rehabilitation Research Center and the informed consent from participants were obtained.

Our study showed that SIS AC improved the functionality of bladders by decreasing the detrusor pressure, improving detrusor compliance, and avoiding renal deterioration. It has no gastrointestinal complications and metabolic abnormalities and enteric mucous. SIS-regenerated bladder had good compliance and capacity achievement, with contractile activity and radiologic and histological results. When large bladder tissue is in demand, acellular matrix grafting and cells are necessary. Biological material alone can facilitate tissue regeneration in partial AC. In our study, patient A completed 36 months of follow-up. The implanted bladder showed adequate capacity with preservation of renal function. This indicated that proper use of SIS during partial AC does not lead to fibroblast deposition, scarring, graft contracture, and a reduced reservoir volume over time (Fig. 45.3).

SIS has excellent host compatibility and remodeling function. Unlike enterocystoplasty, SIS AC is likely to expand gradually post-operatively. Thus, early bladder cycling by clamping the catheter intermittently is necessary for facilitating bladder remodeling. The anticholinergic agent is needed. Our study showed that MBC increased at the 1-month, and significantly at 3 and 12 months post-operatively, indicating that a strict regimen of post-operative CIC may also facilitate bladder remodeling. Urodynamics found that patients with reasonable bladder capacity tend to have good outcome. We reasoned that bladders with adequate basic capacity could be better expanded. Careful selection of patients with low-grade pre-operative UUT deterioration and watchful surveillance of post-operative bladder cycling are vital. The animal studies showed that non-seeded SIS could regenerate three layers of bladder tissues [22]. Other studies demonstrated the smooth muscle cell infiltration, vascularization and innervation in early stages, and did muscle bundle formation later. In our study, there was a smooth, epithelialized inner surface in the absence of the implanted materials 6 weeks post-operatively (Fig. 45.4).

Cystoscopy showed the surface of the grafted wall to be paler with a tendency to shed from the regenerative area 1 month post-operatively. It was difficult to distinguish the grafted wall from native bladder 6 months post-operatively. The complications of SIS AC are bladder stones and bladder rupture. No stone formation was observed in our study, possibly due to good urine drainage after surgery. The histological results partly support the theory of urothelial cell migration and structural properties of the original bladder wall may be transferred into the newly formed portion of the bladder. In our surgery, the SIS-grafted bladder was covered by perivesical tissue. Suprapubic catheter and perivesical drainage were all left *in situ*.

45.7 Summary

The work investigating TE patches using a variety of scaffolding materials continues to blossom, both in the laboratory and in the clinical setting. In bladder augmentation, SIS provides seemingly good results. These intermediate results are encouraged. The long-term follow-up to determine if these moderate-term good results are maintained is necessary. Whether or not non-seeded scaffolds are a better long-term source than cell seeded constructs remains to be seen, but at least at this juncture the technology with SIS is promising.

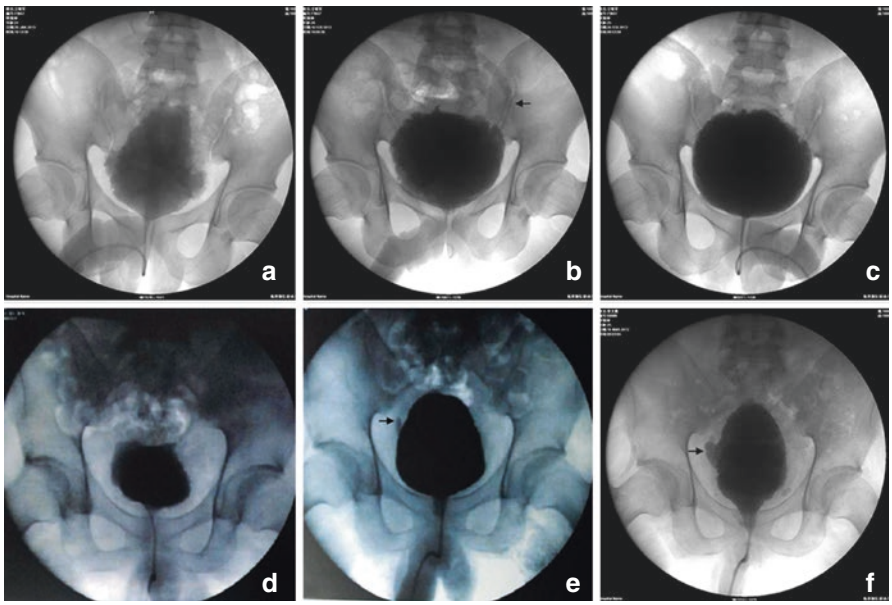

Fig. 45.3 Cystogram in patients with SIS bladder augmentation. (**a–c**) Cystogram in patient H. (**a**) Before surgery. (**b**) 1-month follow-up (dark arrow indicates vesical drainage). (**c**) 6-month follow-up. (**d–f**) Cystogram in patient A. (**d**) Before surgery. (**e**) 3-month follow-up (dark arrow indicates ureteral stump). (**f**) 36-month follow-up (dark arrow indicates ureteral stump). Ureteral stump was left at the time the ureter and bladder were disconnected when performing URI

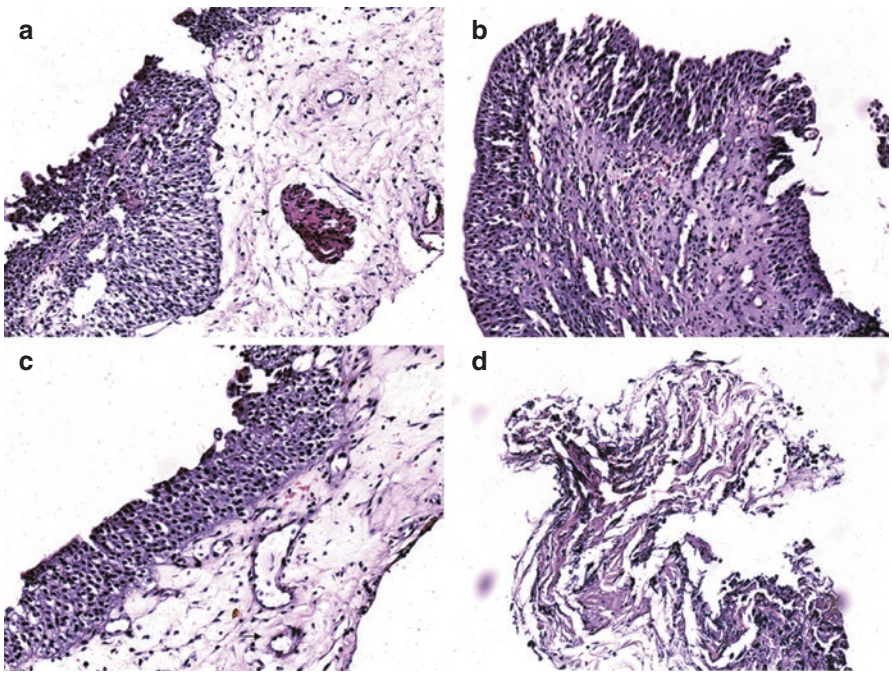

Fig. 45.4 Morphologic analysis of implanted engineered bladder in patient H. (H & E, reduced from 100). Cystoscopic biopsies of implanted engineered bladders 1–3 months post-operatively show extent of regeneration. (**a**) Inflammatory infiltration with follicular aggregation is present in lamina propria 1 month post-operatively. (**b**) Multilayered transitional epithelium fully covering regenerative bladder wall 6 weeks post-operatively. (**c**) New blood vessels proliferating into abundant connective tissue and fibroblasts 3 months post-operatively. (**d**) Connective tissue is regular without evidence of acellular scaffold 3 months post-operatively. Small amount of muscular fibers was observed

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Part XIV

Substitution/Diversion

Bladder Substitution in Neuropathy

46

Julian Shah

46.1 Introduction

Bladder substitution is a technique in which the native bladder is replaced by an alternative. Much depends upon the appropriateness of surgical removal of the bladder and the indications for the bladder removal. The number of these procedures has been falling over the past decade [1, 2].

46.1.1 Bladder Removal

The removal of the bladder will depend upon the aetiology of the bladder pathology. Thus, a bladder substitution is necessary when the bladder is removed in total for lesions such as cancer or interstitial cystitis or whether the bladder is thick walled, small, painful and does not store.

46.1.2 Augmentation vs. Substitution

In patients with neuropathic bladders there has been an increasing tendency to use augmentation techniques rather than bladder substitution since even if there is bladder wall thickness ureteric obstruction the bladder can be augmented rather than removed. The ureters are tunneled into the native bladder in a sub mucosal tunnel without involving the muscle of the bladder wall thus avoiding the need for a more major surgical reconstruction and using the bladder as a back plate for reimplantation. Therefore the less invasive double clam augmentation ileocystoplasty with ureteric reimplantation should have largely replaced bladder substitution for the patient with a small capacity thick walled high pressure bladder.

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However, if there an indication to remove the bladder such as for cancer related to long term catheterisation or neuropathy with bladder pain or for a small capacity bladder and for a patient with bilateral ureteric obstruction a bladder substitution can be an alternative.

46.1.3 Issues to Consider

There are several issues with regard to a bladder substitution that are essential, which are as follows:

- The decision as to how to perform bladder drainage
- Continence
- Ureteric drainage
- Capacity

If a patient can self catheterise urethrally and it is just an issue of bladder storage then the bladder can be substituted with standard techniques of bladder substitution using either large or small bowel depending upon the surgeon's preference. De-tubulisation of any bowel segment is necessary in patients with neuropathy to avoid high pressure contractions causing both incontinence and the risk to the upper urinary tract.

Whether or not the operation is supratrigonal or subtrigonal will very much depend on the state of the ureters but in the majority of patients with neuropathic bladders if a substitution is to take place then ureteric separation from the native bladder is necessary with reimplantation of the ureters.

46.1.3.1 Continence

If the patient is able to self catheterise urethrally much depends upon continence. Thus, if a patient has a competent outlet and the bladder is to be substituted intermittent catheterisation can continue to be conducted after a substitution. However, if the outlet is incompetent much depends upon whether or not continence can be provided. This will vary as to whether or the patient is male or female.

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_46

Continence in the Male

In a male the most effective option for continence where both bladder neck and sphincter are incompetent is an artificial urinary sphincter and this can be placed at the time of a bladder reconstruction.

Continence in the Female

In a female patient much depends upon the state of the outlet. If it is a matter of hypermobility with sphincter weakness a colposuspension procedure may be sufficient to provide continence to allow intermittent catheterisation or alternatively an autologous sling. A mesh could be placed later if the substitution does not provide sufficient continence but it is preferable to perform any anti incontinence procedure at the same time since this reduces morbidity for the patient.

46.1.3.2 Bladder Neck Closure [3–5]

If the outlet is deemed uncorrectable because of significant urethral destruction then the bladder neck should be closed and this can be performed either trans abdominally at the same time as the reconstruction or trans vaginally in a female patient with a martius fat pad laid over the urethral reconstruction.

If the patient requires a substitution cystoplasty with voiding through the urethra using intermittent catheterisation then this is a relative straightforward procedure.

46.1.3.3 Continent Diversion and Mitrofanoff [6–8]

The alternative if the outlet cannot be catheterised is to perform a Mitrofanoff procedure. The Mitrofanoff tube can be made either using an appendix if available or using a Monti tube(s) using small bowel either with one, two or even three segments of bowel depending upon the patient's body habitus and need for length.

If the bladder is removed then the Mitrofanoff tunnel will be into the neobladder. The optimum site for the Mitrofanoff opening needs to be chosen according to the patient's habitus. Often the umbilicus is chosen which is a cosmetically acceptable situation. Alternatively the opening from the Mitrofanoff can be placed anywhere that is accessible to the patient. If the outlet is competent and a Mitrofanoff is performed this is preferable for the patient since there is then double access to the neobladder. If however the bladder neck is closed for whatever reason then the only access to the bladder will be by the Mitrofanoff channel. This has to be recognized as a potential cause of problems should bladder access be necessary because of stone formation or need for an endoscopy (or open surgery) [9]. An endoscopy can be performed down the Mitrofanoff channel using either a paediatric scope a Millerscope or a flexible instrument depending upon the caliber of the Mitrofanoff but these should be ideally made to accept at least a 14 French catheter and preferably a 16 French catheter with a good long anti leak tunnel.

46.2 Pre-Operative Preparation

Prior to any form of a bladder substitution or orthotopic or continent diversion the patient should be appropriately assessed with video urodynamic studies. Ultrasound scanning of the urinary tract and preferably a CT urogram should be performed to understand the anatomy of the urinary tract. If there are duplex ureters it is important to recognize this and reimplant them appropriately to avoid the potential of missing an ectopic ureter.

The patient should be advised about the nature of the reconstruction and taught about intermittent self catheterisation either urethrally if necessary or via the Mitrofanoff so they are fully aware of the potential risks and complications. The patient should be suitably counselled by a well- trained health professional.

46.3 Complications of Continent Diversion [10–12]

Continent urinary diversions with Mitrofanoff catheterization channels are not without their problems. The risk of complications has been quoted variably between 50 and 80% implying that there are complications that may require surgical intervention such as stenosis of the Mitrofanoff tract particularly at the skin level, stenosis down the tract or leakage. Each of these may require further surgical intervention.

With have an experience of using bulking with Macroplastique for injecting Mitrofanoff tubes that leak. This can be beneficial to avoid any major surgical intervention. The alternative is to reimplant the Mitrofanoff once again into the orthotopic bladder. For skin level stenosis usually skin reconstruction at the site of the tube will provide benefits. However, it is highly likely that over a long period of time that some complications will occur with Mitrofanoff tubes since they are not nature's creation and the human body will have a tendency to scar contract any abnormal situation. Thus complications should not be a cause of surprise but should be what one would expect given the circumstances.

46.4 Follow-Up [2]

The patient who undergoes surgical reconstruction will require long term follow-up. In the initial period after any reconstruction this will involve closely supervised post-operative care and regular reviews over the first year after any reconstruction. Imaging should take place of the upper urinary tract within three months of any surgery to ensure that the kidneys are draining. An ultrasound scan will then take place at least annually with an associated consultation with a specialist team.

46.5 Where to Conduct the Surgery

Reconstructive surgery should take place in a specialist centre where there is an experience in complex surgery and in particular where there is an experience in treating patients with neuro disability.

46.6 Incidence of Substitution of the Urinary Tract

The number of patients undergoing a substitution cystoplasty or orthotopic reconstruction is relatively few and most centres will have the experience of relatively few patients. If one considers that there are only 112 urinary diversions per annum in spinal cord injury patients in the United States of America the number of patients undergoing orthotopic reconstruction will be relatively fewer [13].

For example augmentation cystoplasty is less commonly performed than it used to be. In the United Kingdom the number of clam augmentation ileocystoplasties for patients with overactive bladders in general has dramatically fallen over the last few years due to the use of Botulinum toxin.

46.7 Bowel Function

There is reported to be no "relevant changes in bowel movements … after resection of 55–60 cm of ileum if the terminal ileum and the ileocaecal valve were left intact" [14].

46.8 Impact on Quality of Life

There is no doubt that reconstructive surgery can provide a significant improvement in quality of life for patients who are incontinent of urine, particularly where there is risk to the upper urinary tract.

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Urinary Diversion in Neurological Disease

47

Julian Shah

47.1 Introduction

Patients with neurological disease will have a tendency to develop abnormal bladder function as has been previously described in the previous chapters. This neurogenic bladder dysfunction gives rise to both storage dysfunction and difficulty with bladder emptying. This is often associated with urinary incontinence. The principles of management, which has been described in the previous chapters, are to maintain low pressure storage within the bladder and be able to empty the bladder to completion. If this can be achieved by "normal" or balanced voiding then this is the optimal management. If not intermittent catheterisation is the primary method of management for draining bladders that will not empty with some form of therapy to stabilize the bladder so it can store under low pressure.

When the patient is unable to perform intermittent catheterisation this does cause difficulties in terms of management. The only alternative then being some form of a urinary diversion.

The simplest diversion is a urethral catheter. The urethral catheter, which has been able for decades, is an effective means of draining the bladder. Thus, unfortunately is not satisfactory for long term purposes.

The consequences of long term urethral catheterisation are urethral irritation, urethral inflammation, scarring within the urethra and the effects upon the meatus. It females the natural progression of long term urethral catheterisation is inflammation, dilation, erosion and urethral destruction. With long term catheters in females often the urethra will be damaged to the point at which it will leak urine and the catheter may pass with the balloon inflated. Thus, long term urethral catheters in females are entirely inappropriate.

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In males urethral catheterisation will inflame the penile meatus and can and does cause urethral cleavage giving rise to iatrogenic hypospadias. Thus, even in males one would imagine a long term catheter is acceptable, it is not. Long term catheters should be avoided at all costs in the urethra. Thus if a urethral catheter is to be placed it should be a small, around 12–14 French, and left in for relatively short periods before a definitive decision is made as to how to manage the bladder. If the bladder management is to be with catheterisation then suprapubic catheterisation should be chosen as the ideal.

The indication for using long term catheters very much depends upon a number of factors. If intermittent catheterisation cannot be performed then a long term catheter can be chosen. Usually patients, who cannot self catheterise have difficulties with catheterisation because of limb dysfunction due to a high level of a spinal cord injury, after a stroke or Parkinson's disease or MS. It is usually limitation of a patient's physical abilities to do self catheterisation or patient's preferences that leads to long term indwelling catheterisation. Many patients will choose long term catheterisation because in some respects it is an expedient and avoids the need to pass the catheter on a regular basis and does give more freedom to the patient inspite of the down side of having a long term catheter. Thus, if the patient has tried to do intermittent catheterisation without success then long-term catheterisation should be discussed with the patient and if the patients desires and is happy to have a long term catheter placed it should be a suprapubic catheter.

47.2 Suprapubic Catheters [1]

The suprapubic catheter is used to drain the bladder by its placement above the pubic symphysis directly into the bladder. This is a procedure which should be undertaken in the operating theatre under sterile conditions. If the bladder can be easily filled endoscopically and the bladder punctured

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_47

without difficulty using a trocar and cannula system or Seldinger technique and a size 16 French catheter placed then there is no reason why this should not be undertaken in the operating room.

If there is any concern about placement of a suprapubic catheter because of body habitus or previous abdominal surgery the placement of a suprapubic catheter must be undertaken in the operating theatre using endoscopic guidance plus a radiologist with an ultrasound scan machine to check that there is no bowel interposed between the abdominal wall and the bladder. This will then avoid the risk of bowel perforation caused by the placement of a suprapubic catheter which can be a catastrophic complication. This can be avoided by using ultrasound scan guided catheter placement.

Long term catheters are not without their problems but they do work effectively in many patients and many patients have an improved quality of life because of the reduction in need for attention of to the catheter, the freedom of having to self catheterise.

Long term catheters can be associated with either comfort and effective long term drainage or may be associated with significant complications.

We have a policy in our unit of changing the catheter every 6 weeks. A coated catheter with silicone - a size 16 is usually the most effective catheter and can be easily changed. Clear silicone catheters can sometimes be more difficult to change because when the balloon is deflated there is a ridge that is wider than the catheter caliber and can make it more difficult to remove the catheter. If the catheter is changed every 6 weeks this does reduce the risk of encrustation and blockage for many patients. We also have a policy or what we call "catheter clamping" that is to encourage the patients to clamp the catheter using a flip flo valve to allow the bladder to fill and empty. By performing this once or twice a day for an hour or two this will preserve bladder capacity. Although there is some controversy over this issue of distention of the bladder there is no doubt that preserving capacity has benefits in the long term both in terms of reducing inflammation within the bladder and maintaining capacity particularly if the patient at some point wishes to return back to intermittent catheterisation.

Patients with suprapubic catheters will have inflammation at the site of entry into the abdominal wall. This sometimes will discharge and it is quite normal as a reaction to the presence of the catheter and it should not be a cause for concern. There is no need to treat any discharge with antibiotics unless there is local inflammation.

Recurrent infection can occur in patients with long term catheters. Patients often are colonized with organisms but they do not need treatment if the patent is asymptomatic. We use a policy of self-start antibiotics therapy. The patient keeps antibiotics at home to take immediately should symptoms of infection develop such as feeling unwell, increasing spasms or incontinence or increase smell of the urine. Short courses of antibiotics will often resolve these symptoms and the patient then will remain asymptomatic. The resistance of organisms is reduced by short course of antibiotics.

Patients may develop stones within the bladder as a consequence of long term catheterisation. If this occurs they will be treated appropriately by a lithotripsy.

There has been concern about the development of cancer within patients' bladder who are long term catheterised. The risk is in the region of 6% at 20 years. We did have a policy in our centre of performing regular cystoscopies on an annual basis and we were able to demonstrate at 12 and 19 years that we did not pick up any cancers over that period in long term catheterised patients. This does not mean however that cancer cannot develop sooner since they earliest we have discovered cancer related to long term catheterisation is 15 years. These cancers tend to be squamous cell and can be aggressive. Thus any change in the patient's symptoms and in particular blood in the urine should be taken seriously in patients with long term catheters particularly being when they have been there for many years. If bladder cancer develops this needs to be treated according to basis principles of cancer therapy usually with a cystectomy and diversion.

The alternative to long term catheterisation or reconstruction for patients with significant disability is a urinary diversion [2, 3].

It is interesting to see how frequently this operation is performed and there is an article published [4] which demonstrated that over a period of almost 20 years in the United States only 112 ileal conduits were performed per annum in patients with a spinal cord injury. This demonstrates that the operation is relatively uncommonly performed even in a first world country. Thus, the number of patients who would need to have a urinary diversion is relatively small.

In our own experience the patients who need a urinary diversion have ether had significant problems with long term suprapubic catheterisation, or patients who cannot do intermittent catheterisation and are usually significantly disabled. Thus, a patient of quadriplegia with a high level lesions whose catheters cause significant problems would be a good candidate for a urinary diversion. Patients with spina bifida also fall into this category particularly where the bladder is small capacity and there is significant incontinence and where reconstructive surgery is not appropriate. Thus, a urinary diversion should be considered as being at the top of the list for patients who have fallen into these category.

The decision to operate however very much depends upon a number of factors and that is:

- Patient's age
- Gender
- A degree of disability
- Morbidity
- Obesity

In patients, who have spina bifida with significant physical disability where there is a limited access to the abdominal wall a urinary diversion can be a difficult procedure. Placement of the ostomy can also be difficult.

47.3 Cutaneous Vesicostomy [5]

This is a technique which can be used in children with spina bifida as an alternative to ileal conduit diversion or catheterization.

47.4 Ileal Chimney

It has been suggested in the past that an ileal chimney is an effective way of performing a urinary diversion connecting a segment of ileum to the dome of the bladder and to the abdominal wall. This is a relatively infrequently performed procedure and it is not always an effective way of draining the bladder (in the authors's experience) since there can be stasis of urine and this can cause infection and mucus retention and it is not something that should be generally recommended.

47.5 Ileal Conduit Urinary Diversion

An ileal conduit urinary diversion, which has been available for decades, is an effective method of draining the urinary tract in patients who are considered suitable for a urinary diversion.

The question is whether or not the bladder should be removed at the same time of the diversion. The recommendation is that unless there is a significant indication for taking the bladder out the bladder is best left behind since this will reduce the length of the surgery and the morbidity. For the majority of patients with a retained bladder no sequelae developed. In about 25% of patients there will be the development of pyocystitis which may later need either a cystectomy or some form of drainage procedure which can be performed in females using a Spence procedure of a fistula created creating between the bladder and the vagina. Thus, it can be seen in 100 patients 75 will be spared of having the additional cystectomy, which is probably not necessary in many [6].

If a cystectomy is necessary for pyocystis is can be performed later through a pfannenstiel incision extraperitoneally as a relatively minor procedure taking approximately an hour with a relatively short in-patient stay [7].

A urinary diversion using an ileal conduit is a the gold standard for a urinary diversion. The ureters can be joined to the ileal tail either separately or together using a Wallace 66 technique. However, it is the surgeon's preference as to how that technique is achieved. A urinary diversion is a very effective way of draining the urinary tract. The indications of a urinary diversion are:

- Failure of other form of urinary drainage in particular long term catheterisation
- Bladder pain in the presence of a long term catheter
- Failure to conduct self-catheterization where long term catheterisation is not preferred
- A small capacity thick-walled bladder with upper tract dilatation due to bladder wall thickness in which a reconstruction is not considered appropriate.

It is preferable for patients with major disability to undergo surgical treatment in a centre with experience in managing patients with neuro disability. These patients are not straight forward and should not be managed in general wards unless there is a major experience in managing patients with major disability. This particularly applies to avoid the deveopment of pressure sores area. In the post-operative period many patients will require a period of time on a high dependency unit. Patients, who have undergone abdominal surgery may develop prolonged ileus and this may require a longer period of hospitalization.

Once recovery has occurred from the surgical intervention then all patients with urinary diversions should go onto long term follow up. This would consist of at least an annual ultrasound scan of the urinary tract and a consultation. There should be measurement of loop residual to make sure the ileal conduit is draining satisfactorily since a retained residual can be associated with infection and stone formation.

Provided the operation is successful, a stoma is created of a sufficient length and the patient does not develop any other untoward compilations then long term follow up is usually straight forward. However complications can occur in association with an ileal conduit such as ureteric obstruction, urinary tract stone disease, recurrent urinary tract infection, stomal prolapse, stomal stenosis, stomal retraction and para stomal hernias and incisional hernias. Each of these complications should be treated according to standard principles, which can be applied to any patient's group with an ileal conduit.

Where an ileum is not appropriate for a urinary diversion colon can be used but the preference is to use the ileum.

One other issue that should be considered in patients who are significantly disabled who both have urinary dysfunction and bowel dysfunction is a colostomy, which can be performed at the same time as an ileostomy procedure. It can be of a benefit to the patient of having both the procedure performed at the same time. This may require the involvement of both the urologist and general surgeon.

47.6 Minimally Invasive Surgery [8]

In the future robotic/laparoscopic techniques may be used for performing such surgery to reduce the overall morbidity once experience in these techniques becomes widespread.

47.7 Quality of Life

Urinary diversion improves the urinary quality of life but not the overall quality of life according to Guillotreau et al. [9].

47.8 Conclusion

A urinary diversion is often necessary for patients with neuropathic bladder dysfunction. The simplest most common urinary diversion is a long term suprapubic catheter. The use of bowel urinary diversion is relatively infrequently used even in developed countries and are unlikely to increase in a number over time. Thus any surgical procedure, which involves urinary diversion should be conducted in specialist centres where there is experience in both the surgical technique in particular the management of patients with disability where there are additional issues which need a multi-disciplinary team input.

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Part XV

Surgery for Bladder Outflow

Surgery for Bladder Neck/Urethra

48

David Manuel Castro-Diaz and Barbara Padilla-Fernandez

48.1 Surgery to Decrease Outflow Resistance

48.1.1 Sphincterotomy

Surgical sphincterotomy aims to decrease outlet resistance in order to protect the upper urinary tracts, reduce risk of urinary tract infection, and diminish rates of autonomic dysreflexia in the face of neurogenic DESD [1]. Indications include worsening hydronephrosis, vesicoureteral reflux, autonomic dysreflexia and recurrent UTIs believed to be due to poor bladder emptying. This procedure is performed transurethrally with the goal of dividing, either completely or partially, the fibers of the external urethral sphincter [2]. It has been described using either electrocautery [3] or laser energy [4] for division. Typically, the incision is extended at the 12 o'clock position from the mid-prostatic urethra to the bulbomembranous junction. The depth can be difficult to gauge, but early pioneers of the procedure report it should be carried down until the plane of the periurethral venous sinuses is seen [5]. It has been recommended for patients with concomitant bladder neck dysfunction that an additional 6 o'clock incision of the bladder neck be made, as with traditional transurethral incision of the prostate [6]. A large-caliber three-way catheter is then inserted to allow for urinary drainage and continuous bladder irrigation if needed. These are typically removed in 24–48 h post operatively. There have been no randomized trials comparing laser sphincterotomy to the electrocautery approach, but proponents of the laser approach believe that it conveys a lower risk of bleeding.

With the hypertonic sphincter disabled, the detrusor leak point pressure decreases, and dangerously high storage pressures are avoided. Sometimes, a degree of continence can be maintained, though this depends on preservation of bladder neck function and, in men, the degree of prostatic resistance.

Though it can diminish urologic complications of DESD, sphincterotomy is not without risk. Pre-surgical counseling should include discussion of possible hemorrhage, erectile dysfunction, retrograde ejaculation, urethral stricture, and fistula formation. Practical problems include chronic incontinence, which can lead to unpleasant odors, soiled garments and, more concerning, skin breakdown and the development of ulcers. In Pan's series of 116 sphincterotomies, no patient required transfusion. Other authors have noted a rate of clinically significant bleeding of about 10%, but also state that transfusion is rare [2, 7]. When Yalla et al. compared men undergoing sphincterotomy at the 12 o'clock position vs. the 3 and 9 o'clock positions, he found a 9% transfusion rate in the 3/9 group and gave no transfusions in the 12 o'clock group [8]. Contemporary reports on erectile dysfunction rates vary from 3 to 7% after sphincterotomy [2, 9] with rates of urethral stricture between 3 and 13% [10].

Moreover, sphincterotomy should not be considered a permanent solution for DESD and these patients do require ongoing monitoring for recurrent infections, upper tract deterioration, and recurrence of DESD. Pan et al. described a series of 84 primary sphincterotomy patients from their center, treated from 2001 to 2009 [11]. Of these, at mean follow up of 6.4 years, failure of initial sphincterotomy—classified as patients who experienced urosepsis, persistent or recurrent DESD, upper tract dilation, or worsening renal function—occurred in 68% of patients. Mean time to failure after the primary procedure was 36 months. The success rate of secondary sphincterotomy in these patients was 43%, with improvements in storage and emptying parameters being preserved on average for 80 months. Lockhart reported failures in 25% of his 60 all-male sphincterotomy series, defined as persistent symptomatic UTIs or high residual urine volumes greater than 100 mL, and found that the majority of

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_48

failures were in patients with poorly contractile bladders, such that the bladder was not able to empty even in the face of reduced outlet pressure [12]. In his series, Lockhart reports 50% success in men with detrusor areflexia, but 84% success in men with detrusor hyperreflexia.

48.1.2 Bladder Neck Incision

Some urologists combine external sphincterotomy with some degree of bladder neck incision in their attempt to surgically correct DESD. Bladder neck incisions are classically performed with two incisions at extending from just distal to the ureteral orifices, though the bladder neck fibers, and into the prostatic urethra. Studying the specific contributions of bladder neck incision toward maintaining upper tract health and avoiding urinary tract infections in patients with neurogenic bladders is difficult, as few authors describe the extent to which their external sphincterotomy incises the bladder neck and/or whether they combine a formal, separate bladder neck incision with that procedure. To date, there are no published series in which bladder neck incision is the only therapy used for treatment of DESD.

In their series of adult patients followed at a spinal cord injury rehabilitation center, Vainrib and colleagues identified 97 patients who underwent "bladder neck incision and external sphincterotomy" (BNI/ES) [13]. Of these, 47% required at least one revision BNI/ES. Common indications for revision included autonomic dysreflexia, elevated detrusor pressures, recurrent UTIs, elevated PVRs, hydronephrosis, and new-onset renal insufficiency. In their series, the decision to undertake ES alone vs. BNI alone vs. a combined procedure was based on urodynamic and radiographic findings that indicated the site of lower urinary tract obstruction. However, they note that early in their series, all patients underwent combined BNI/ES, as that was the initial standard of care in their practice. Patient data were reviewed in aggregate, without differentiation between those who underwent BNI and those who did not, nor those with obstruction primarily at the bladder neck vs. primarily at the external sphincter. Of note, success rates (53% at 106 months) and durability of improvement (105–148 months) were similar to other studies in which BNI was not a standard accompaniment to ES.

The most common complication was bleeding, though no patients required blood transfusion. Additional complications unique to BNI include bladder neck contracture, though Vainrib reports that none of the 46 patients requiring revision in his study had a bladder neck contracture or urethral stricture. Additionally, the desire to target BNI to bladder neck obstruction may encourage the use of more frequent videourodynamics, which may add expense to the care of the patient cohort and may not correlate with substantial improvements in outcomes.

48.1.3 Stents

External urethral stents are an attractive alternative for those who cannot perform CIC and wish to avoid the perceived risks of sphincterotomy. They have been demonstrated to decrease voiding pressures and residual urine volumes [14]. In addition, they are potentially reversible, as the stent can be removed, and do not carry the risk of erectile dysfunction seen with more invasive procedures. Both temporary (removable) and permanent stents exist [15].

The most commonly used stent is the UroLume permanent stent (American Medical Systems, Minnetonka, MN), a tubular woven mesh stainless steel alloy. The radial mesh exerts a strong, continuous, outward force against the urethral lumen to maintain patency up to 42 Fr. This implant was first designed for the treatment of BPH, but has been investigated in the neurogenic bladder population as well. Indeed, a 20-year series was published by the Spinal Cord Injuries Centre of the UK's Royal National Orthopedic Hospital, where the UroLume stent was first used for DESD patients [16]. Their series included 12 patients with suprasacral SCI who underwent UroLume stent placement from 1988 to 1990, ranging in age from 26 to 65 years. Of these patients, six have functional stents and preserved renal function at 19–21 years post-operatively. Of the remaining six patients, two had early encrustation requiring stent removal, one died of infection at 7 years post-insertion with a functional stent, and two were lost to follow up at 1–3 years with functional UroLume stents in situ. The final patient developed bladder cancer and required cystectomy and urinary diversion 14 years after stent insertion.

However, of the six patients with UroLume stents in place, further procedures have been required. Five required bladder neck incisions for development of VUR (4), UTI (4), hydronephrosis (1), and bladder stones (1). The authors believe that the bladder neck dyssnergia was likely present prior to stenting, but disguised by the DESD and only revealed once this aberrant voiding pattern was resolved with stent placement. Their patient with bladder stones also required cystolitholapaxy. The mean time to these complications was nine years. Two of the patients with VUR required sub-ureteric bulking agent injection for resolution of VUR. The authors do report that erectile function was not altered by stent placement for any of these men and that they were easily able to perform cystoscopy when indicated while the stent was indwelling. The group at the Spinal Cord Injuries Centre reports a substantial decrease in maximum detrusor pressure from 94 cm/H_2O (range 76–112) preoperatively to 67 cm/H_2O (range 36–88, $p < 0.01$) after 20 years.

While intended for permanent use, successful removal of the UroLume stent has been reported [17]. The stent can be removed by grasping a wire at least 2 mm from the edge and gently pulling to collapse the stent mechanically, which

elongates and narrows the stent, allowing for removal. Alternatively, the tines can be dissembled in situ and removed piecemeal. If there is substantial epithelialization, preliminary disruption of this tissue with either elecrocautery resection or laser ablation may be required. In their series, the North American Study Group reported a 13% stent removal rate, mostly for stent migration. Of these patients, 90% went on to undergo successful placement of a subsequent stent.

Permanent stents may cause problems if epithelialization is poor or if a hyperplastic response leads to urethral occlusion. Concern for these risks has prompted interest in temporary urethral stent placement as an attractive alternative. Game et al. describe their experience with temporary urethral stenting in their 2008 series [18]. From 1994 until 2003, they treated 147 men with mean age of 41 years with temporary urethral stents placement for neurogenic DESD. All patients were either unable or unwilling to perform CIC and were interested in an alternate form of bladder management. They placed the stents endoscopically: 121 with lidocaine jelly in awake patients, 9 with neuroleptanalgesia, and 17 under general anesthesia. Patients were monitored 1 and 3 months post operatively, and then every three months thereafter. They had four cases of hypertensive crisis due to autonomic dysreflexia and one case of urethral bleeding. Early postoperative complications were seen in 21%: UTI with symptoms in 10%, urinary retention in 5% (requiring suprapubic tube placement in five patients), and gross hematuria in 3%. One patient had a stroke related to hypertensive crisis and ultimately expired; another suffered bradycardia and resuscitated cardiac arrest. Later complications included symptomatic UTI in 8% and difficulties using condom catheters in 7%. Stent migration was reported in 29% of patients. Mean PVRs were > 200 mL lower in the postoperative setting (mean 298 mL preoperatively vs. 81 mL post operatively, $p < 0.01$). Upper tract dilation rates were lower in the postoperative period as well (three patients vs. 12 patients, $p = 0.03$). The majority of stented patients leaked urine into a condom catheter (70%) as their preferred method of bladder management.

Ultimately, the mean duration of temporary stenting was 10 ± 16 months. Upon stent removal, encrustation was observed in 3% and granulation tissue in 10%. All stents were easily removed per the authors' report. In their series of 147 patients, a permanent urethral sphincter stent was placed in 63% of patients after removal of the temporary stents. The authors describe temporary stenting as useful bridge therapy to allow time for upper motor function to improve after an acute injury and/or to test the therapeutic intervention of urethral stenting prior to placing a permanent stent. At this time, the Memotherm (Angiomed, Karlsruhe, Germany) and Diabolo (Coloplast, Humlebaek, Denmark) stents remain commercially available.

Stents are not without complications, including encrustation, migration, erosion, recurrent UTIs, overgrowth of granulation tissue and possible obstruction. Chancellor et al. reported stent migration rates of 30% and urethral erosion rates of about 2% at 5 years after insertion [14]. Moreover, removal of urethral stents can be challenging. Some authors also raise the theoretical possibility of autonomic dysreflexia due to stretch of the urethral wall; however, this complication appears to be rarely borne out in practice. Ultimately, as with all neurogenic bladder patients, those with urethral stents will require attentive follow up to assess urodynamic parameters, upper tract health, and stone risk, and infectious complications.

48.2 Surgery to Restore Continence

48.2.1 Urethral Slings: Men and Women

48.2.1.1 Pubovaginal Slings

Pubovaginal slings have long been the treatment of choice for both adults and children with neurogenic SUI since they can achieve urethral compression and also give support [19]. Continence rates are high (85–90%), and it is an established procedure in women with the ability to self-catheterise because a high tension is given to the sling [20–23]. It was initially described in 1907 using autologous gracilis or pyramidalis muscle [24], but it was reintroduced with modifications in 1978 by McGuire and Lytton [25].

Several materials have been used for the pubovaginal slings [26]:

- Autologous graft materials: the tissue is harvested from the same patient's body, which offers maximum biocompatibility and excellent incorporation into the host tissue with minimal inflammatory reaction [27, 28]. The most commonly used sling material is the anterior part of the rectus muscle fascia [29, 30], but other techniques have been described as the fascia lata sling obtained from the lateral tight [31, 32] and the vaginal wall harvesting the midline vaginal mucosa and the underlying periurethral support structures to create a sling initially described by Raz [33] and modified afterwards by several groups [34, 35].
- Allograft materials: the tissue is obtained from human cadaveric donors and needs lyophilization (freeze-drying) and sterilization by gamma radiation in order to decrease the risk of transmission of infectious agents to the recipient [32]. Slings usually belong to fascia lata and rectus muscle fascia.
- Xenograft materials: the tissue is transferred from one species to another. The diisocyanate processing method is used to suppress the immune response and decrease the

risk of infection. Common xenografts for pubovaginal slings are bovine pericardium, porcine bowel, and porcine dermis [36, 37].

- Synthetic prosthetic materials: loosely woven polypropylene mesh is the most commonly used material because it allows for the best ingrowth of the host tissue and macrophage transition [28, 38, 39]. However, erosion/exposure and infections are more often reported with these materials [40].

The outcomes after fascia lata allograft slings are controversial [41, 42] and some authors have reported the allograft-associated transmission of s human immunodeficiency virus in one in eight million cases and prion infections [43, 44], and autograft rectus muscle fascia is more commonly used [45, 46]. Comparing to synthetic or allograft slings, a longer operating time due to graft harvesting and repositioning of the patient is needed, and associated morbidities of the harvesting site such as bleeding and infection may appear [47].

For the harvesting of the rectus fascial graft in women, a Pfannenstiel incision 2 cm above the pubic symphysis is performed with the dissection carried down to the rectus fascia. A 2×10^{-12} cm rectus fascia graft is marked out and the edges of the graft are dissected and freed from the underlying rectus muscle. Running sutures of polypropylene are stitched onto each end of the graft with the sutures left long. After placement of a urethral catheter and hydrodiseccion of the vaginal mucosa, the bladder neck is identified by palpation of the catheter balloon. A vertical incision is made from 2 cm below the meatus to the level of the bladder neck. Then, lateral vaginal flaps using a combination of sharp and blunt dissection are created, which are lifted up with Allis clamps and the ischiopubic ramus is palpated. A window is created in the ipsilateral endopelvic fascia using Metzenbaum scissors pointing upward, toward the ipsilateral shoulder, and opening the space between the endopelvic fascia and ischiopubic rami that has previously been hydrodissected. The ends of the graft sutures are tied to the blunt ends of the trocars and brought out through the vaginal incisions. By careful guidance behind the pubis, the trocars are brought out through the abdominal incisions. A cystoscopy with a 70-degree should be performed to check for any urethra or bladder injury before pulling out the trocars completely. The two free ends of the sutures are then pulled up while keeping an artery forceps or scissors in place between the fascia and periurethral tissue. The suture ends are tied together above the rectus fascia with a finger placed underneath the knot to avoid excessive tension [47].

Although it is more common to identify neurogenic SUI in women, puboprostatic fascial slings have also been successfully used in men [19, 20, 48–50]. An abdominal approach is commonly used (especially if the procedure is going to be performed during an augmentation cystoplasty) beginning with a midline incision extending from the symphysis up to the umbilicus and opening the space of Retzius. The endopelvic fascia is then identified and incised to obtain the plane between the urethra and rectum, and a right angle clamp is passed under the urethra avoiding injury to the rectum. A free graft of rectus fascia measuring approximately 10 × 1.5 cm is obtained from the edge of the incision and it is then passed around the urethra just distal to the prostate. The ends are secured to (ipsi- or contralateral) Cooper's ligament using 1-0 polypropylene [20].

48.2.1.2 Midsuburethral Synthetic Slings

Midsuburethral synthetic slings are the choice of election in female non-neurogenic SUI, but they have been introduced later in neurogenic patients [51]. They have gained popularity because surgeons avoid operative morbidity and complications of harvest site pain and infection of the autologous fascia slings. Early and late continence rates in this subgroup of patients is comparable to the general population, although the need of catheterisation is higher conditioned by patient's neurogenic disorder [52, 53]. De novo overactive bladder can also appear that can be managed with antimuscarinics and botulinum toxin injections [52, 54].

Some authors have reported their experience with polypropylene male urethral slings with good continence results but with persistent need of intermittent catheterization and also reporting infections and technical problems in the initial cases [55, 56]. Avoiding an abdominal incision and performing the surgery with a perineal approach may allow to undergo an outpatient procedure. New-onset catheterisation rates are lower than with puboprostatic fascial slings and infections or other complications may be minimised in specialised centres [55, 57, 58].

Polypropylene mini-slings have been also used in both men and women with neurogenic SUI and with previous need of intermittent catheterization with good continence rates [59], but there is still limited data on long-term continence rates.

48.2.2 Artificial Urinary Sphincter: Men and Women

Artificial urinary sphincter (AUS) has been frequently placed in children with myelomeningocele. It consists of three components: a pressure-regulating balloon, an inflatable cuff, and a control pump. The advantage of AUS placement in this population is that patients may be able to void spontaneously and avoid intermittent catheterization [60, 61]. On the other hand, up to 34% of children without augmentation cystoplasty prior to AUS placement may require augmentation

due to deterioration of bladder dynamics after AUS placement [60, 61].

A systematic review by Farag et al. analysing the success rate of the surgical treatment of neurogenic SUI and the individual effectiveness of each surgical modality (AUS, slings and bulking agents) included 30 studies involving 849 patients (525 males and 324 females) with a median age 21 years old (range 3–80). The AUS studies reported a longer mean follow-up, highly significant success rates compared to urethral bulking but no statistical differences compared to suburethral slings, and higher reoperation rates [62].

The complication rates and reoperation rates are higher than in non-neurogenic patient groups (up to 60%), so it is advisable that patients are conscientiously informed about the success rates as well as the complications that might occur after the procedure [62–64]. Reinterventions are commonly due to infection, urethral atrophy or erosion, and mechanical failure [65, 66].

Some authors prefer to implant the AUS at the bladder neck rather than bulbar urethra because those AUS are larger and urologists would have a lesser chance of damaging the device with a large-bore rigid cystoscope if needed. Similarly, it is less probable to damage the device for patients on intermittent catheterization regimes (with direct trauma on the urethra) and those wheelchair-bound (who can develop perineal pressure sores close to the bulbar urethra) [61]. No statistically significant difference has been found when comparing this position to the common bulbar urethral devices in terms of success, failure or reoperation rates, but the complication rates were lower [62]. In France, an expert consensus has been reached on the use of bladder neck implantation in male neurogenic SUI patients [67].

Laparoscopic placement of AUS in the bladder neck/periprostatic in patients with neurogenic SUI has been described, and even the robot-assisted transperitoneal procedure in six men with neurogenic SUI secondary to spinal cord injury with no revision or complication reported after a median follow-up of 13 months (range 6–21) [68].

Another modified technique has been described, replacing the intrascrotal pump with a port that was used 6 weeks after surgery for inflating the implant with the exact amount of fluid needed to achieve continence during a video-urodynamic control. This port can be also accessed later to adjust the filling if urinary leakage reappears and it can be even used if leakage of the implant is suspected by injecting contrast media into the system [69]. The majority of patients with neurogenic bladder dysfunction secondary to spinal cord lesion need intermittent catheterization, and they sometimes lack the dexterity and mobility to handle the pump, so this method could be a good alternative in this subgroup of patients.

48.2.3 Urethral Bulking Agents

Patients with spinal cord lesions below the level of the sacral micturition center commonly experience sphincteric incompetence which leads to stress urinary incontinence (SUI) [62]. In these patients, mild stress urinary incontinence can sometimes be treated with procedures to increase the bladder outlet resistance. One such procedure is endoscopic placement of urethral bulking agents [70]. This treatment is minimally invasive and can usually be performed in the office [71]. Agents include bovine cross-linked collagen and dextranomer hyaluronic acid.

Collagen injections for intrinsic sphincter deficiency in neurogenic bladder patients were first described in the late 1980s by Shortliffe et al., who treated 17 adults and achieved 53% improvement or cure of SUI [71]. A 1995 study by JK Bennett and colleagues described their experience with 12 neurogenic bladder patients [72]. Their group reported injecting the crosslinked collagen under the urethral mucosa so as to increase the coaptation of the urethral walls, enhancing the competence of the patient's sphincter and inhibiting SUI. In their series, 64% were substantially improved or cured with regard to their SUI. The mean pretreatment Valsalva leak point pressure was 60 cm H_2O, which improved to 117 cm H_2O in post-operative patients. None of the patients experienced significant complications during the 24 month follow up period and all were able to continue CIC. These studies and others like them [73, 74], support the use of collagen as an alternative or adjunct to pharmacotherapy, surgical reconstruction, or implantation of a prosthesis in the management of SUI in the neurogenic bladder patient.

Lightner et al. included spinal cord injured women with sphincteric deficiency in their trial of cystoscopic injection of dextranomer hyaluronic acid, and found this product to be "neither safe nor efficacious," with a high rate of pseudoabscess (11%) and de novo urge incontinence (46%), as well as poor patient-reported efficacy (only 33% with durable improvement in voiding symptoms). The group recommends against the use of dextranomer hyaluronic acid for periurethral injections [70].

In their meta-analysis, Farag and colleauges reported 27% success with bulking agents at a median of 30 months follow up [62]. The six studies that used bulking agents included 126 patients (65% male), with collagen used in 74% and polydimethysiloxane in 22% [62]. The median reported complication rate was 4% with a 12% reoperation rate. One third of patients received three or more injections of bulking agent prior to study completion. Success rates were greater in patients whose neurogenic SUI was treated with a urethral sling or artificial urinary sphincter, rather than a bulking agent, however both had higher rates of complications, and the AUS group had a median 51% reoperation rate. The authors conclude that the AUS is the gold standard for

neurogenic SUI, with a urethral sling being a reasonable second-line option.

48.2.4 Bladder Neck and Urethral Reconstruction

The bladder neck is a critically important structure in preventing loss of the urine from the bladder. During bladder filling, the bladder neck must remain closed. It should be also stress competent. These sphincteric properties must become quiet during voiding, reverse their roles, and form a compliant tube through which urine can pass [75]. Regardless of the primary cause, urine leakage in the absence of a detrusor contraction is the definition of an incompetent urinary sphincter mechanism [76].

Urinary incontinence as a result of bladder neck incompetence is a serious medical, social, and psychologic problem for children, parents, and caregivers. Causes of bladder neck incompetence in children include neurogenic bladder (myelodysplasia, sacral agenesis, or other congenital or acquired spinal cord injuries), the exstrophy-epispadias complex [77], cloacal malformations, bilateral or single ureteral ectopia, and trauma [75]. Seventy percent of children with myelodysplasia have an incompetent bladder neck [78]. When urinary incontinence persists after correct anticholinergic treatment and clean intermittent catheterization, bladder neck reconstruction is recommended. It is also recommended in adult patients with urinary incontinence with a congenitally incompetent bladder neck [79], an extremely common and lifelong issue affecting up to 71% of patients who present to transitional clinics [80].

Common findings leading to bladder neck reconstruction are open bladder neck on cystography during low pressure urine storage and abdominal leak point pressure less than 40 cm H_2O based on urodynamic study besides a poor compliance [81].

As suggested by Kropp, bladder neck reconstruction should be performed for achieving continence in patients with normal bladder innervation, normal detrusor muscle function, a prior history of normal voiding, and correctable bladder neck anatomy. On the contrary, bladder neck reconstruction should be performed for dryness when patients have faulty innervation, an abnormal or non-functioning detrusor muscle, numerous prior failed bladder neck reconstructive procedures for continence, and the prior initiation of an intermittent catheterization program [75].

An ideal BOP for neurogenic bladder patients should achieve the following [82]:

- socially acceptable dryness, which is commonly accepted as a minimum of 3–4 h dry-interval with intermittent catheterizations;
- not to compromise bladder volume, bladder function or upper urinary tract;
- allow easy catheterization and a pop-off mechanism at high pressures;
- long-term reliability,
- easy performance with a short learning curve.

Various techniques have been described: Young-Dees-Leadbetter (YDL) [83–85], the Kropp repair [86], the Pippi-Salle [87], and the modified Leadbetter/Mitchell (LM) repair [88]. Studies reviewing these bladder neck reconstruction techniques report reasonable continence rates ranging from 50 to 85%. Other authors have reported case series with different techniques, for example bladder neck reconstruction by lengthening, narrowing and tightening the bladder neck with a combined tubularized posterior urethroplasty and circumferential fascial wrap [89]. Robot-assisted bladder neck reconstruction has been described [90, 91].

In 1986, Kropp et al. [86] reported their experience with the creation of a bladder tube allowing a catheter to be passed into the bladder but avoiding urine leakage. For this purpose, a rectangular bladder pedicle flap is outlined on the anterior bladder wall and based upon the bladder neck. Afterwards, the bladder is completely separated from the bladder neck and a tube is created rolling the flap over a Foley catheter. This tube is then attached to the bladder creating a broad submucosal tunnel between the ureteral orifices, and the bladder is closed down to and around the bladder neck. They also described the development of the tubularized bladder flap from the posterior bladder wall. Several modifications to simplify Kropp procedure have been described, for example incomplete detachment of the bladder neck [92], placement of the detrusor tube in a shallow [93], excision the muscular layers of the tube down to the mucosa [94].

Later, Pippi Salle et al. [87] developed another surgical technique using an anterior bladder wall flap which was sutured to the posterior wall in an onlay fashion creating a flap valve mechanism. One of the main differences with the previous repair is that two parallel incisions were made in the posterior trigonal mucosa to expose the muscle, and both ureters were reimplanted using a crosstrigonal method. They have also described their own modification of the technique in order to avoid formation of urethrovesical fistula and/or partial necrosis of the intravesical neourethra like creating a widened base to the urethral flap, a lateralized flap in those patients with previous bladder surgery and discontinuation of routine ureteroneocystostomy [95].

Specifically in incontinent children after staged exstrophy/epispadias reconstruction, a detrusor wraparound was first described as the Heiss loop by Gil-Vernet in 1953 and Woodbourne in 1968, and then popularized as the anterior detrusor loop by Mollard in 1980 [96, 97]. Kurzrock et al. also described a similar technique in a patient population

with neurogenic incontinence in 1996 [98]. These reports preceded the development of the Mitchell modification of Young-Dees-Leadbetter bladder neck reconstruction, also known as Leadbetter/Mitchell repair [98]. The main steps in this technique are the transverse opening of the bladder neck followed by the performance of parallel incisions lateral to the trigone almost reaching the ureteral orifice and leaving a posterior strip of trigone. The anterior bladder wall is retracted cranially and the urethra is then tubularized with the completion of the bladder closure. The newly tubularized neourethra is then coapted and supported by an autologous strip of demucosalized detrusor flap that is wrapped once circumferentially around the bladder neck.

Bladder neck reconstruction may be complemented with augmentation cystoplasty if the patients have a poor bladder compliance even after anticholinergic treatment [99], end filling pressures >40 cm H_2O (or >80 cm H_2O) and/or hydronephrosis grade 3–4 [100]. Both procedures may be done in the same surgery or cystoplasty may be indicated and performed afterwards in order to avoid mucous interfering with catheter drainage, bladder stones, metabolic acidosis, vitamin B12 deficiency, and risk of death from bladder rupture with sepsis and shunt contamination and/or future malignancies [101]. Some authors also describe bladder neck reconstruction after augmentation cystoplasty with/without a catheterizable channel [102]. It is also possible to combine bladder neck reconstruction with a sling procedure. A study by Snodgrass and Barber reported that patients undergoing LM procedure plus fascial sling were significantly less likely to require pads postoperatively than those with a sling alone [103]. In high-volume centres, combination of different surgical techniques as primary continence procedures is feasible and achieve reasonable success rates [104].

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Part XVI

Other New Procedures

Bladder Re-innervation Procedures

49

Karl-Dietrich Sievert

Abbreviations

C	Cervical
DO	Detrusor overactivity
DR	Dorsal root
DSD	Detrusor sphincter dyssynergia
EMG	Electromyography
L	Lumbar
LUT	Lower urinary tract
S	Sacral
Th	Thoracic
UMND	Upper motor neuron disease
VR	Ventral root

49.1 Introduction

In 1967, Carlsson and Sundin reported on a 4-year-old spina bifida patient who underwent rerouting of the thoracic 10–11 ventral (motor) roots to S1–S2 ventral roots. After eight months of recovery, reflex micturition and bladder sensation appeared [1, 2]. Despite this previous interest in nerve rerouting to reinnervate the neurogenic bladder, it was Xiao and Godec who further pursued this concept [3]. Studies were first done in animals, confirming that the bladder could be reinnervated by a somatic nerve and that reflex micturition could occur [4]. This was followed by reports of some early clinical success in humans with spina bifida [5].

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Spinal cord injury (SCI) is a devastating condition affecting approximately two million people worldwide, with an estimated 11,000 new injuries reported every year. The median injury age, estimated at 26 years, results in lifetime costs over $1Mp/p [6]. The urologist's foremost critical challenge is to preserve renal function, minimize complications and improve the SCI life quality that is severely burdened by incontinence, inability to micturate, frequent self-catheterization, daily medication, and recurrent urinary tract infections. SCI patients ranked regaining bladder and bowel function even higher than the ability to walk [7]. These statistics make it highly convincing to research and investigate any opportunities to provide SCI patients with the possibility to "normalize" their life.

SCI level of severance and completeness of lesion determines the level of dysfunction in the urinary bladder and sphincter complex. Upper motor neuron disease (UMND) above the level S1/S2 (Th12/L1 or *complete SCI*) typically leads to detrusor overactivity (DO), often combined with hypercontractile external sphincter, known as detrusor-sphincter-dyssynergia (DSD) [8, 9]. Recommended treatment consists of frequent clean, intermittent catheterization (CIC) and pharmacotherapy to preserve low pressure and continence; DO treatment options include antimuscarinics and the recently-approved onabotulinumtoxinA [8, 10, 11]. These treatments can be ineffective; in some cases, invasive surgery (e.g. bladder augmentation) may be recommended [8, 10]. Thus far, the only possible minimal-invasive approach to initiate spontaneous voiding seems to be sacral nerve stimulation including deafferentiation of S2–S4 dorsal roots [9].

Animal and human models involving nerve rerouting (NR) have been previously described in the early 1900s [12], however, no tangible long-term results have been reported. In 1994 and 1999, Xiao presented NR below the SCI in animal models. This "skin-CNS-bladder" reflex pathway centers on a basic premise: after surgery, the L-dermatome is stimulated (e.g. scratching sending a signal to resulting nerve). Underlying assumptions elucidate that motor axons of the somatic-reflex-arc provide the potential to regenerate into autonomic preganglionic nerves, re-innervate the blad-

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_49

der's parasympathetic ganglion cells and transfer somatic-reflex-activity to the detrusor muscle [13].

In 2003, a 67% success rate in a human study, where 15 male SCI patients reported regaining satisfactory bladder control and emptying functions, 12–18 months after ventral root (VR) microanastomosis (L5–S2/3) [14]. A transformation was reported from detrusor hyperreflexia and high detrusor pressure to near-normal storage pressure and synergic voiding validated by urodynamics (VU) [14]. In a 2006 *review*, Xiao further reported a remarkable 88% success rate in 92 SCI patients who presented with hyperreflexic or acontractile bladders, 81 of which regained bladder control within one year postoperatively [13].

As an alternative option at one clinic, early bilateral sacral neuromodulation was offered [3], but only prior to any pressure changes in the bladder while VU were recorded. This provides only a very small time frame to implant modulators to be effective; whereas it was suggested that there is no time limit in between the SCI and the performance of the surgery [13], making the potential of the presented method more attractive.

Long-lasting treatment remains not only an imperative mission, but a health care necessity. Based on these encouraging results and the concurrent NIH-sponsored clinical trial [15], our multi-disciplinary team offered SCI patients an individual rehabilitation surgery to determine efficacy and safety [16], ability to normalize lower urinary tract (LUT) functionality, capability to initiate almost residual-free micturition without catheterization and improve bowel management.

The second group, who is supposed to benefit of the ventral root (VR) microanastomosis (L5–S2/3) was supposingly those patients with a spina bifida [5].

About 5% of patients have spina bifida occulta [17]. Rates of other types of spina bifida vary significantly by country from 0.1 to 5 per 1000 births [18]. On average in developed countries it occurs in about 0.4 per 1000 births [19]. In the United States it has affected about 0.7 per 1000 of births, and in India about 1.9 per 1000 of births [20]. Part of this difference is believed to be due to race with Caucasians at different risk factor and partly due to environmental factors [21]. The major issues those patients have to deal with are bladder and bowel control, including incontinence, urinary tract infections and poor kidney function [22].

49.2 Background

Recently, bridging peripheral nerve defects became a possible therapeutic approach to minimize defective functioning [23]. Thus far, NR has been reported primarily on the level of cervical injury to regain arm, hand/finger and even facial nerve function [24]. NR was later proven in an "intact spine" animal model where it was demonstrated that crossover nerves from slow-to-fast muscle despite mixed response results [23]. Thus far, NR has been reported primarily on the level of cervical injury to regain arm, hand/finger and even facial nerve function. NR was later proven in an "intact spine" animal model where it was demonstrated that crossover nerves from slow-to-fast muscle despite mixed response results. What is relatively new is the goal to regain function for internal organs after SCI, which can be segregated into two primary approaches: additional SCI bridging to regain CNS control or rerouting to establish a new reflex arc.

LUT innervation highly depends on a complex network of sacral, pontine and suprapontine micturition centers where the spinal cord facilitates a pathway for voluntary initiation, inhibition and modulation [8]. Relatively few publications of bladder innervation exist despite this area of research initiating immense interest with neurologists, urologists and SCI researchers [8]. Even for patients with spina bifida, the improved function of the lower urinary tract would be an amazing improvement for their QoL. Regaining control of LUT and bowel function would be considered a milestone, not only for the patient's life quality, but to lighten the burdened healthcare system.

49.3 Published Studies

Encouraged by published results, in four centers in Europe and the US, patients were offered a treatment with low risk and an expected outstanding success rate [5, 14]. In those centers the surgery was offered for the two main indications: SCI or spina bifida. The protocol replicated the original [14], with the benefit of combined urodynamic and neurophysiological evaluations both pre- and intraoperatively by a multidisciplinary team. To secure the highest likelihood of success, the initial describer discussed in three out of four centers, the protocol, selected the best SCI/spina bifida candidates that demonstrated sufficient distance above the level required for the somatic-reflex-arc (although Xiao surmised that all SCI/spina bifida types would be suitable as long as spine level toward bladder/sphincter endorgans were not damaged [13]) and supervised some of the surgeries. Because the outcome seems to be even more difficult to be proven in the indication of spina bifida, the Tampa center [25] enrolled patients into a randomized, prospective, double-blinded trial of the Xiao procedure in 20 children undergoing spinal cord detethering. The detethering was either performed alone or combined with the Xiao procedure.

Published theory established the shortest distance of axonal regeneration from anastomosis to pelvic ganglia, estimating complete nerve regeneration within 12–18 months [13]. More common neurological theories support that axons regenerate at a speed of about 1 mm/day [26, 27]. With regard to animal model and regeneration distance of 120 mm (S2 VR to bladder) [3], 11 months were estimated approximately for 150 mm [4, 13].

Minor positive secondary outcomes, which underline that the anastomosis was successfully performed by an

experienced neurosurgeon were noted [28], but the published significant results regarding voluntary initiated micturition by scratching were not observed or demonstrated [6, 7]. Only Peters et al. were able to report in their patients with the spina bifida, with their definition of treatment success, seven of 13 (54%), since one other patient was only voiding with 47% efficiency related to retethering [29]. This overall outcome for either indication is not as convincing as the initial publication of Xiao et al. [5, 14, 30] with a success rate of over 80% to gain the capability of sufficient voiding by activating the dermatome reflex.

49.4 Why Doesn't It Work?

49.4.1 Animal Model Investigations

In an attempt to better understand why "below SCI CNS-bladder reflex re-routing" was not as successful in the published studies of the western countries, the previously published electrophysiological animal experiments were scrutinized [3, 4]. One reason might be that Spinal Cord Transection (SCT) was performed just prior to the final evaluation (≥1 year postoperative [3]; ≥2 years postoperative [4]) (confirmed by Xiao CG at AUA, 2012) and the NR was performed in the first step. Similarly, Lin et al. reported subsequent SCI in a canine model nerve pathway innervation above the SCI level using an abdomen-to-bladder reflex arc [31], where he noted that this method was used because "paraplegic animals were extremely difficult to take care of for a long period". However, electrophysiological studies included intravesical pressure recordings before and after paraplegia onset that occurred 12 months after initial nerve graft surgery in six of ten dogs [31]. Copious numbers of animal models followed, all using different reflex arcs and different roots and all matching the success rate as reported by Xiao et al. [14]. It can be concluded that the method undertaken in both of the Xiao and Lin animal models significantly altered any validation that the rerouting theory would lead to the "assumed outcome." For the correct set up to validate the onset, the accurate model would necessitate rerouting after the initial chronic SCT effect to the LUT. Similar requests would be necessary for a spina bifida model, which have been reported in recent years [32, 33].

49.4.2 Human Investigations

Review of recent literature, both previous to and post, of the described pathway show different human bladder reinnervation models. Prior to Xiao CG's report, Livshits et al. demonstrated success in 8/11 patients using an approach by bridging the SCI (Th11–12 anastomosed to S2–S3) with regained sensitivity within 12 months [34]. This approach seemed to be proven in a later anatomical investigation [35]. In 2009 Lin et al. reported functional satisfying results using the Achilles tendon-to-bladder reflex below the SCI [36]. Within 12 months in 9/12 patients mirrored the success rate reported by Xiao [13]. More interestingly, Lin et al. published a case report with a similar approach and results [31], where they reported complete functional bladder rehabilitation (storage and voiding) two years after the initial surgery but it seems to be worthwhile mentioning that the patient had an indwelling catheter for 1.5 years. Voiding was initiated by scratching the Th10 dermatome. These high efficacy rates have not been replicated elsewhere, despite the describer travelling and performing/supporting this approach in SCI and spina bifida patients all over the world [25, 37, 38]. Xiao did not publish, since the initial reports related to SCI and spina bifida, any further peer reviewed long-term follow-up data. He only stated in a review of NR mentioning more than 300 SCI patients without any objectively detailed follow-up evaluation a further improved outcome. However the author noted the difficulties to follow-up the patients because of the required outlying distances to reach SCI patients [30].

Tuite et al. [25] stated after their prospective randomized double-blind study in patients with spina bifida that the results are predictably more difficult to interpret due to the presence of partial bladder and bowel function in most patients, which makes his prospective, randomized, double-blind study even more important [25]. Rasmussen et al. looked in addition into the influence to the bowel but couldn't find in their patients, with supraconal SCI a significant improvement 18 months after the Xiao-procedure (segmental colorectal transit times, anal sphincter pressures and rectal capacity did not change, and no change was seen in NBD score (median 13.5 (baseline) vs. 12.5 (follow-up), $P = 0.51$), St Marks fecal incontinence score (4.5 vs. 5.0, $P = 0.36$) and Cleveland constipation score (6.0 vs. 8.0, $P = 0.75$) [39].

49.4.3 Explanation Why the Early Couldn't Be Reproduced

Some critics might argue that antimuscarinics were continued throughout the study for some patients, thereby perhaps inhibiting the aimed outcomes, however, the patient group was heterogeneous. Sievert et al. reported in the early phase about one patient during VU electrostimulation 13 months post-NR, demonstrated a detrusor contraction leading to low-flow micturition [40]. These results were not reproducible afterwards. Interestingly, in the group of patients who stopped antimuscarinics immediately after the surgery and two patients that never took any antimuscarinics before and throughout the study, establishing results similar to other patients [37]. A similar setting can be found in those patient Rasmussen et al. [39] followed up for 18 months. To protect the upper urinary tract, EAU guidelines recommend anti-

muscarinic therapy in DO patients for long-term efficacy and safety that may be even combined for maximized outcomes (LE1A) [41]. The primary effect of antimuscarinics is to relax smooth muscle to decrease the detrusor contractility to slow the critical pressure of 40 cm H_2O. There is no published evidence that antimuscarinic use might negatively influence nerve regeneration/growth. If this effect would exist, other results in those patients who never received antimuscarincs or the other patients during follow-up would be expected, making the argument that no antimuscarinc treatment should be administered invalid.

In the published case after SCI, who had to undergo surgical re-exploration 3 years after the Xiao procedure revealed that the anastomosis was in anatomical continuity but neuroma formation had prevented reinnervation [41]. Another case reported by Peters et al. that one of the patient developed a re-teathering, which reduced the efficacy to their understanding to 47% [29]. It remains unclear if patients who are in the growth phase might stress the nerve anastomosis that the outcome is under risk or even situations like the effect of the untethering and possible retethering might lead to the previous effect which vanished as Tuite et al. theorized and that in the spina bifida effect was already gained by the untethering procedure itself.

49.4.4 Similar Results, Same Procedure?

With regard to Kelley after the initial recruitment of two patients [15], where patient selection and surgical procedures were also directly supervised by Xiao CG, no further SCI patients were enrolled because of unsatisfying outcomes. In other US centers, three patients were operated on with a similar lack of success at William Beaumont Hospital, in Royal Oak, Michigan [not published], one at Lousianna State University, Shreveport [unpublished case report from Dr. Mata], and one at the Children's Neuroscience Institute, St. Petersburg, FL [41]. They noted comparable minor intermittent positive results, but not the overwhelming previously published outcome [6, 7]. The colleagues from Denmark even visited CG Xiao prior to their start of their enrollment. Similar to the recent presented long term outcome of Sievert et al. [37] Rasmussen et al. concluded: "no clinical relevant effect on the lower urinary tract" [39] and "no effect on bowel function in subjects with supraconal SCI" [42] with a follow-up of 1.5 years.

In the published single case report, the patient with incomplete SCI underwent a re-exploration 3 years after the initial Xiao procedure demonstrating the nerve anastomosis transformed into a neuroma [41]. Neuroma occurrence might be the result of improper healing in the area of the nerve anastomosis or could have been caused by 10 year old boy's growth, causing increasing tension at the local anastomosis [41]. Important differences are noticed: Surprisingly the young patient initially reported the sensation of urge to urinate all the time and even to urinate after scratching (months 6–12). These are strong signs that the boy was an incomplete SCI patient, but we have no neurogenic evidence for motoric or sensoric response after the hemorrhage caused by the neuroblastoma. If the response to the scratching was due to rerouting, the effective endorgan reinnervation would not have resulted in the neuroma development. These arguments make this case report more likely to be an incomplete SCI and therefore best compared with those published spina bifida cases. While some success has been noted with spina bifida cases [43], these two patient groups shouldn't be combined because, in the spina bifida patients, the connection between the spinal cord and brain is still intact, and therefore, bear no direct comparison.

If the patients with spina bifida of the two hospital locations are somehow different and even the interpretation of the outcome, this data needs to be analyzed separately. Although the number of patients who underwent the NR in both centers are similar, the interpretation of the resulting data is different and definitely not easy. Tuite et al. has the objective benefit of the setting of their study set up: prospective, randomized, and double blind. The resulting data, although the number of patients is not high and the difference within the two groups is the age with the resulting better QoL for those, which received in addition to the detethering the NR, was better, but all other aspects were insignificant [38].

The NR surgery can be technically and safely performed especially in those patients with a SCI. Some modulation of bladder function occurred. Related to some temporary improvements, it can't be decided if these results occurred because of NR or nerve transection that cannot compensate the complexity of the brain. Beside the minor effect of a rhizotomy-like effect, it seems that bladder function in its complexity cannot be initiated by somatic-to-autonomic reflex. That would explain why the effect is seen in spina bifida patients, where the CNS is intact and the spinal cord functions as wiring between different CNS levels that are mandatory to control storage and voiding. It needs to be mentioned that the NR in patients with spina bifida can be a challenge related to the anatomical given situation of scar tissue incapsulating often even thinner nerve roots as in a normal situation of the os sacrum similar to the SCI patients where the injury lies above the approached surgical field **(pictures of SCI surgery and the spina bifida to compare those both)**. Positive effects in the bowel might be explained by (1) bowel autonomic innervation (2) reduced pathological effect of SCI related to rhizotomy-like effect to nerve roots

affecting the bowel, primarily the colon and rectum [44, 45]. Another explanation might be that reinnervation takes place as previously discussed which demonstrates minor effects such as bowel movement [42], but that rerouting and scratching/local stimulation might not be strong enough to normalize storage and voiding [46].

49.4.5 Potential Study Limitations

With all the published data in the group of patients with SCI (n = 25) and those with spina bifida (n = 23), all authors see the main limitation in the number of patients they recruited. It needs to be mentioned that in all the centers involved, the multi-disciplinary teams, who took care of those patients, are all highly recognized specialists in their field. Even further improvements such as the fixation of the endangered anastomosis to the dura was noted up by Xiao. Whereas in patients with SCI no real side effects were reported beside some minor improvements, which were significant in those of CG Xiao, in those patients with spina bifida although the results are still not as significant as those reported by CG Xiao's and—this has to be highlighted as well—in the prospective randomized double-blind study of Tuite et al. [41] the QoL improved compared to those who did not undergo the additional NR. However, on the other side the effect of foot drop worsened in the spina bifida patients.

In the two main publications the final outcome is differently assessed. Tuite et al. is able to compare the outcome of two groups, which are a result of the randomization [38]. Why the group of those with the additional NR is younger in average remains unclear and the resulting effect of the reported better QoL. However, in the primary domain, the outcome is the equivalent in both groups, which resulted to the final conclusion that there is no benefit in the additional NR, beside the detethering in spina bifida patients. In comparison the group of Peters et al. [29] reported an average improvement of 50%.

Similar to the findings of Tuite et al. [41] it seems that in the most of the patients Peters et al. [29] followed over the years, the "reproducible reflex" seems not to initiate the supposed reflex anymore which Peter et al. interpreted as a reconfiguration of the micturition centers in the brain similar to when a child learns to void independently and the brain suppresses this reflex similar to what is seen in toilet training.

Lastly it is not possible to directly compare data of the four major publications and statistics with those that support the outcomes of the centers within China, because SCI reports [13] were briefly reported in a review, not an original article publication and others were published in Chinese [18, 35, 47–50].

49.5 Conclusions

Although intraspinal nerve rerouting is a technically feasible and safe procedure, none of the patients with SCI reached the primary goal of voluntary micturition, even with an extended follow-up of up to 7 years.

For the group of spina bifida patients the discussion might not be final, but the outcome of the prospective randomized double-blind study of Tuite et al. will be difficult to argue [41], which is strongly supported in editorials [51]. Any performed NR surgery should be reported in a centralized database including an objective and suitable follow-up. New animal studies investigating uni- vs. bilateral rerouting after complete spinal cord injury, followed by a standardized treatment protocol in a highly-controlled study environment, are necessary to further investigate and validate the potential. Until the effectiveness of this surgical approach can be confirmed in clinical trials, this procedure should not be performed on further SCI and spina bifida patients.

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Other New Developments: Use of Stem Cells and Gene Therapy

50

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50.1 Introduction

Since 1990 the Nobel Prize in Medicine was awarded to Donnall Thomas for his discoveries concerning cell transplantation in the treatment of human diseases, our understanding of what stem cells are, how they work, and what their clinical potential is, has increased tremendously. In the last 15 years medical societies and associations, such as the International Society for Stem Cell Research (ISSCR) and EuroStemCell, have been founded and several scientific journals have been exclusively dedicated to promote stem cell research and applications.

Stem cells have the potential to revolutionize medicine [1]. According to the United States National Marrow Donor Program (NMDP), the world's largest hematopoietic cell registry lists several blood cancers, such as acute myelogeneous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myelogeneous leukemia (CML), juvenile myelomonocytic leukemia, Hodgkin-lymphoma, as well as Non-Hodgkin lymphoma (NHL), that can be successfully treated by blood stem cell transplantation. Although inherited immune disorders, such as Wiskott-Aldrich syndrome, inherited metabolic disorders, such as Krabbe disease and Hurler syndrome, and hemoglobinopathies, such as thalassemia and sickle cell disease, can be treated by blood stem cell transplants [2]. Blood stem cell transplantation is a proven and essential therapy for more than 70 diseases [2], which is well established in standard of care protocols for hematopoietic cell transplantation [3]. In 2013 the worldwide network for blood and marrow transplantation (WBMT), affiliated with the WHO, have announced the one millionth blood stem cell transplant [4]. The number of stem cell publications is skyrocketing with an annual growth rate of 7% [5].

The invention of induced pluripotent stem cell (iPSC) technology was awarded with the Nobel Prize in Medicine to Shinya Yamanaka in 2012, which is one of the main landmarks of stem cell medicine. IPSC technology bypasses the need for embryos and bears the promise of unlimited supply of patient-matched (autologous) pluripotent stem cells. Between 2008 and 2013 the annual growth rate of iPSC publications was 77%, and iPSC ranges among the most often cited topics in medicine [5].

Stem cell therapies are progressively entering clinical reality. According to the US National Library of Medicine registry ClinicalTrials.gov, the world's largest clinical trial database, there are currently more than 500 clinical studies in phase II, and almost 100 phase III studies, that are recruiting patients for stem cell therapies [6]. Among the phase III clinical studies, most trials assess hemato-oncological diseases. However, some of the pivotal studies assess the value of stem cell application in non-oncological scenarios, such as stroke, myocardial infarction, cardiomyopathy, bone fracture, scleroderma, end stage liver disease, and multiple sclerosis [6].

Gene-therapy, meaning the therapeutic delivery of nucleic acids into a patient's cell to treat a disease, is another game-changing technology in medicine, for which several Nobel Prizes were awarded, and which is believed to redesign future clinical reality [7]. According to ClinicalTrails.gov there are currently 63 phase II and 7 phase III studies recruiting patients for gene therapy studies [8]. Most of them assess gene therapy in hematological or oncological diseases. However, some of them evaluate gene therapy approaches in

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_50

non-oncological diseases, such as Parkinson's disease or diabetic neuropathy [8].

Despite the almost enthusiastic environment surrounding stem cell research and gene therapy, both technologies have not really yet succeeded into functional urology—at least on a translational level [9]. Of course, there are hundreds of publications on stem cells and lower urinary tract function. However, looking into what really matters, excluding reviews and redundant information, including setting the parameters "clinical trial" or "clinical study" using the US National Library of Medicine search engine PubMed, there are only very few studies that have investigated stem cell applications in benign urological conditions. The only relevant stem cell applications in functional urological diseases so far have been in incontinence and erectile dysfunction (ED)–both of which can occur in neurogenic patients. Currently, Clinicaltrials.gov lists 6 phase I, 6 phase II, and 1 phase III clinical trials assessing stem cell application in urinary incontinence with no clinical trial assessing gene therapy in urinary incontinence, 12 phase I, and 6 phase II clinical trials assessing stem cell application in ED, and one phase II clinical trial assessing gene therapy in ED. To the best of the author's knowledge, no clinical trials using either stem cells or gene therapy have been performed or are happening in patients with neurogenic bladder. One phase I clinical trial assessed the role of gene therapy in the overactive bladder syndrome (OAB), which might have some pathophysiological overlap with neurogenic detrusor overactivity (DO), and might therefore be of interest.

Stem cells might be used in the treatment of the neurological disorders underlying a neurogenic bladder. However, the treatment of neurological diseases with stem cells or gene therapies goes beyond the scope of this article, and is summarized elsewhere in detail [10–12]. Further, the use and potential of stem cells in bladder tissue engineering is discussed further [13]. This book dedicates its own chapter for the role of bladder tissue engineering in neurogenic bladder. The following article will focus on stem cell sources. Then, the article will discuss pre-clinical, and clinical data of stem cell and gene therapy in erectile dysfunction and incontinence. And lastly the article will highlight some relevant preclinical studies using innovative new strategies in experimental models of neurogenic bladder.

50.2 Stem Cells

Due to their ability to differentiate into all the different tissues of the human body, including the germ lines, (pluripotency) human embryonic stem cells (hESC) appear to be a perfect source for cell-based therapies. In recent research hESC have been successfully converted into the most various functional tissues, such as insulin secreting islets, cardiomyocytes, and neuronal cells. However, apart from ethical concerns, use of hESC implies the risk of tumors (teratoma) and immune rejection [14, 15]. Due to the shortage of organs for transplantation, and immunological problems of heterologous transplants, as well as the ethical concern about hESC, adult stem cells are gaining further importance. Adult stem cells are characterized by their multi-potency, possibility of autologous transplantation, their relative abundance and possibility of a non-invasive harvesting [16]. Furthermore, adult stem cells are not known to transdifferentiate into a malignant phenotype [17]. However, despite encouraging basic research reports, their transfer into clinical practice according to good medical practices (GMPs) and good laboratory practices (GLP) regulation are still ongoing [18].

Adult stem cells can be obtained from adipose tissue, bone marrow, placenta, amniotic fluid or testes. Bone-marrow derived adult stem cells (BMSC) are the most studied cells. Even though mesenchymal stem cells (MSC) are rare in bone marrow cells, representing about 1- in 10,000 bone marrow cells [19]. These cells can still be isolated in sufficient numbers and be propagated in vitro, so that they provide a good source for cell-based therapy. BMSCs can differentiate into the three different germ cell lines [20, 21]. BMSC harvesting procedure might still be painful for the patient, often requiring anesthesia and may yield in low numbers of MSCs upon processing [22], however, there a new methods which might be soon available that will not be critical related to pain, infection or even need anesthesia. Adipose tissue isolated MSCs have showed multi-lineage potential [23]. These so called adipose-derived stem cells (ADSCs) can be isolated in a less invasive way than BMSCs. Due to the abundance of human fat, they can be harvested to an almost unlimited extent, which makes them very attractive for stem cell application. However, a huge set-back of ADSCs is their lack of definitive cellular markers [24]. Placenta and testis are alternate sources for MSC. Cells isolated from testes show high levels of spermatogonial stem cells (SSC) and characteristics of pluripotency [25]. Amniotic fluid or placenta-isolated stem cells could be differentiated into each embryonic germ layer. Although stem cells account for only 1% of cells in the placenta or amniotic fluid, they can be easily harvested considering the worldwide birth numbers [26].

ADSC can be differentiated in vitro into myoblasts for stress urinary incontinence treatment with the addition of 5-Azacytidin (AZA), which can be confirmed by immunofluorescence for desmin and myosin [27]. BMSCs and smooth muscle cells express the same contractile proteins, so that their potential for myogenic differentiation is obvious [28]. Following BMSC exposure to AZA, myogenic differentiation was induced and confirmed via stem cell surface antigen, intracellular alpha-actin and transcription factor MyoD1 and myosin heavy chain (MyHC) expression.

Therefore, AZA-exposed MSC are more frequently positive in MyoD1 and MyHC than native MSCs [29]. It has been reported that independent to AZA exposure, MSC express smooth and striated muscle antigens, even though AZA increases myogenic differentiation. Since myogenic marker expression was similar in a rat model of periurethral MSC injection in AZA pretreated and untreated cells, differentiation prior to implantation might be dispensable. Differentiation along the urothelial lineage has been reported by direct cell-to-cell contact between ADSCs and urothelial cells [30]. ASDC differentiation in endothelial cells could be demonstrated in vitro and in vivo [31], which might be beneficial for intracavernous injection in ED treatment. Basal cells of the urothelium were shown to possess stem cell properties and could be differentiated into various epithelial directions [32].

Currently a viral-induced pluripotent epidermal stem cell has seemingly opened the possibility to overcome stem cell availability and shortages. Inducible pluripotent stem cells (iPSC) [33] might play a more suitable role in the near future for autologous pluripotent cell applications, especially using the Yamanaka factors in the absence of potential oncogene c-myc as recent publications have demonstrated [34, 35]. Notwithstanding, there continues to be major disadvantages in using these cells due to patient safety and manufacturing generation efficiency. HESCs are still the gold standard in stem cell basic research and are influencing the more GMP-like handling of pluripotency (e.g. the feeder-free stem cell culture in the absence of viruses and murine proteins). IPSCs are a contrary but indispensable tool in pluripotency and differentiation research. At the present time, its safety and abundance in regenerative mechanism use and functional integration without tumorigenicity remains unresolved. Continued basic research in this field is fundamental and absolutely crucial for its self-renewal, differentiation, tissue formation, cell-cell interaction, dedifferentiation and the induction of malignancy. Currently, adult stem cells are still seen to play the most central role in creating truly biomimetic tissue. Its favorable characteristics are their potency, their autologous approach, their relative abundance and their primarily non-invasive extraction. Conversely, its limiting factor may be the potential disease-affected tissue from which they were derived.

Regarding the legal requirements, during recent years the EMA and CAT instigated European Community guidelines for country-specific institutions such as Germany, like the BFA. More enhanced guidelines that clearly articulate "bench- to- bed" protocols must be tested and approved to become part of clinical applications. These protocols can then be used as a basis for cellular therapies and Good Manufacturing Practices (GMPs). These GMP's are critical as cell culture conditions must be regimented to minimize and even exclude risk so that cell changes or cancer cannot occur [18, 36].

The long process from defining the correct source of stem cells or identifying suitable adult progenitor cells with regenerative potential in the respective recipient's tissue to understanding different GMP requirements required for stem-cell culture and differentiation in vitro conditions, while leading to the generation of functional in vivo tissue grafts, have yet to be undertaken.

A further critical step forward would be to establish independent rodent animal models with a more preclinical character using GMP guidelines, which can then be converted into Good Clinical Practice (GCP) clinical trials to ensure patient safety and to verify therapeutic clinical superiority in cell-dependent based therapies. The risks and benefits of cell-based therapies must be also evaluated and compared to already established treatment options.

50.3 Urinary Incontinence (UI)

Most of the studies regarding cell-based therapies for the treatment of urinary incontinence concentrate on the injection of myoblasts or myogenic precursors. Yet myoblast transfer therapy has numerous limitations, including immunological problems and low spread and poor survival of the injected myoblasts [22]. Yiou et al. [37] investigated the fate of muscle precursor cells (MPC) injected into a model of striated urethral sphincter injury and were able to demonstrate that the regenerated myotubes carried acetylcholine receptors associated with a nerve ending and were thus considered to form anatomic motor units. In a study with denervated female rats, Cannon et al. [38] noticed an improved muscle contraction amplitude after the injection of muscle-derived progenitor cells. Several pre-clinical studies assessed the role of stem cell injections in animal models [39]. Most pre-clinical studies were done in rodents, however, monkeys were also used. Urinary sphincter deficiency was induced by electrocauterization and the transaction of the pudendal innervation. Five million green fluorescent protein labelled autologous skeletal muscle precursor cells were then injected into the urinary sphincter. Cells were incorporated into the sphincter and resulted in a long-lasting (12 months) structural and functional restoration of the injured sphincter [40]. In animal models the beneficial effects of stem cell application in stress urinary incontinence were reported for periurthral as well as for intravenous injection [39]. Local injection might be preferable since intravenous administration of cells bears the risk of clogging, and i.v. injected cells will first be localized to the pulmonary capillary bed [41].

Recently Peters and colleagues published their 1-year clinical experience with autologous muscle derived cells (AMDC) for urinary sphincter repair (USR) in women with stress urinary incontinence (SUI). 10–200 × 10^6 AMDCs were injected in the urinary sphincter of 80 women with

SUI. The primary outcome measure was to assess safety by adverse event incidence and severity. The secondary outcome was incontinence evaluation via voiding diaries, 24 h pad test and questionnaires. Adverse events (AE) occurred in 18% of the patients. However, all AEs were mild, transient and either easily treated or self-resolved: seven patients reported dysuria, four patients pelvic pain, three patients pruritus, two patients urgency and two patients hematuria. The authors concluded that AMDC-URS is a safe procedure. The 12-month follow-up rate was 93%. Median stress leaks were significantly reduced in all dosage groups, starting 1 month following injection and maintained during the 12-month observation period, e.g. 16 patients of the 10×10^6 AMDC group (lowest dose) had a median stress leakage over 3 days of 8.5 pre-interventional, which was significantly reduced to 2 after 1 month and 3 after 12 months post-interventional. However, only patients in the highest dose-group (200×10^6 AMDCs) showed a significant reduction in the mean pad weight (86.4 ± 35.3 g before therapy vs. 37.2 ± 24.4 g 12 months after therapy) [42].

Different approaches have also been performed on the reconstruction of urethral sphincter by means of stem cell injection. In the rat model, myogenic stem cells and BMSC survived and remained integrated into the muscular structure for more than 120 days [43]. When application of myogenic stem cells functionality was investigated in the pig model, it was demonstrated that the success is dependent on the amount of applied cells [44]. In a clinical study from Iran [45] injections of autologous muscle derived MSC have been performed for treatment of urinary incontinence in children with classic bladder extrophy and have shown promising results.

Kim et al. [46] worked with a female urinary incontinence rat model and observed an enhancement of closing pressure and leak point pressure (LPP) after local implantation of BMSC. The improved LPP after surgical MSC implantation was also confirmed by the studies of Corcos et al. [47]. In his study a regeneration of external urethral sphincter muscle was verified by the detection of muscle specific antigens. Lee et al. [48, 49] as well as Chermansky et al. [50] obtained equally important results in studies with muscle derived MSC. In studies with ADSC injection it was also verified that rats showed an improved LPP [51] and higher smooth muscle content [52]. Even better results concerning LPP as well as the amount of muscle and ganglia were obtained when ADSCs were injected intramuscularly into the urethra in combination with controlled-release nerve growth factor. There was a significant difference between the ADSC + nerve growth factor group and other groups [53].

However Kinebuchi et al. [54] were not able to verify an improved LPP in their studies with BMSCs. Nevertheless the proportion of skeletal muscle cells and peripheral nerves increased significantly which was also seen by Tamaki et al. [55]. However, with regard to the LPP, there is no significant difference between the injections of muscle derived stem cells and fibroblasts [56]. The first pilot studies show that the path to clinical application is not far away. Carr et al. [57] performed a clinical study with the injection of muscle derived stem cells on eight women. After a 1-year follow-up, five of eight women, showed an improvement of urinary incontinence with one patient achieving total continence. The improvement after the initial injection occurred with a delay of 3–8 months and continued at a median of 10 months. Critics have argued that the study lacks randomization, blinding, dose escalation, and is not significant due to the small number of subjects. Preliminary data from Yamamoto et al. with two patients, and Gotoh et al. with 11 patients, who all received autologous ADSC injections for the treatment of postprostatectomy incontinence, also showed a promising outcome concerning leakage volume, frequency and amount of incontinence and quality of life [58, 59]. However, it is still arguable if the integration and functional regeneration of sphincter tissue, which is verified for the rat model, can also be expected for the human or if stem cells solely react as a bulking agent here.

50.4 Erectile Dysfunction (ED)

In the treatment of ED, the injection of stem cells of different origins into the corpus cavernosum could be a possible approach. In a rat model of cavernous nerve (CN) crush injury, animals were treated with intracavernous injection of ADSC, ADSC-derived lysate, or vehicle only (injured controls). Erectile function was assessed by CN electrostimulation at 4 weeks and penile tissue was collected for histology. Both ADSC and lysate treatments resulted in significant recovery of erectile function, as compared with vehicle treatment. Neuronal nitric oxide synthase (nNOS) content in the dorsal penile nerve was preserved in both the ADSC and lysate group, with significantly higher expression compared with vehicle-treated animals. Significantly less fibrosis and a significant preservation of smooth muscle content was observed in the ADSC and lysate groups compared to injured controls. The functional improvement also after lysate injection implies that ADSCs influence their surrounding through release of intracellular preformed substances or by active secretion of certain biomolecules [60]. Kendirci et al. [61] used BMSC which were either characterized by plastic adherence (typical multipotent stromal cells) or by magnetic-activated cell sorting using antibodies against p75 low affinity nerve growth factor receptor (p75 derived multipotent stromal cells) to treat male rats after CN crush injury. Four weeks after the procedures, erectile function was assessed by measuring the intracavernous-to-mean arterial pressure ratio and total intracavernous pressure during cavernous nerve stimulation. Intracavernous injection of p75 derived multi-

potent stromal cells resulted in a significantly higher amount compared with untreated animals and typical multi-potent stromal cell groups. Though rats injected with typical multipotent stromal cells still had partial erectile function rescue compared with animals that received p75 derived multipotent stromal cells. The use of mesenchymal stem cells transduced with adenovirus containing endothelial nitric oxide synthase (eNOS) seems to be a further option. When pretreated MSCs were injected into the corpus cavernosum, erectile response in aged rats was improved already 7 days after injection, whereas untreated MSCs demonstrated a delayed increased erectile function in aged rats at day 21 [62]. The injection of VEGF164 adenovirus transfected MSCs and unmodified MSCs in a diabetic rat model revealed that 4 weeks post-injection, the erectile function, the content of smooth muscle and endothelium in corpus cavernosum significanly increased compared to the control group (untreated). The VEGF concentration in corpus cavernosum was greater in the VEGF group compared to a group who obtained unmodified MSCs [63]. Considering that VEGF plays an important role in the regeneration of the cavernous nerve [64–66], these data present a promising concept. Other pre-clinical studies exist which assess the value of stem cells in erectile dysfunction models [39]. The group of Maarten Albersen has shown that stem cells migrate to the model's injury site, and this was seen following local (intracavernous) as well as systemic (intravenous) stem cell injections [67]. Current results therefore confirm the potential of MSC injection concepts in the treatment of erectile dysfunction.

Regarding first clinical studies, Bahk et al. reported that intracavernous injection of 1.5×10^7 allogenic umbilical cord blood stem cells in 7 men with type 2 diabetes related ED. They reported on a beneficial effect on erection, as assessed via questionnaires. However, this effect was only short-lived and not durable [68]. Two studies from a private practice setting reported on the use of placental matrix derived MSCs in eight patients with chronic ED and five patients with Peyronie's disease. As summarized recently by Soebadi in an excellent review article, the few clinical studies published to date have a quality "that leaves a lot to be desired", and a major concern is the inappropriate claim of efficacy by commercial stem cell manufacturers [69]. A well-conducted study by Haahr et al. reported the complications and functional outcomes of intracavernosal adipose derived cell injections in 17 men with post-prostatectomy ED. AEs were mainly related to the liposuction procedure, which was necessary for the cell harvest, and all resolved spontaneously. Erection for successful intercourse was achieved in 8 from 17 patients [70]. Yiou and colleagues report on 12 patients with post-prostatectomy ED with escalating doses of 2×10^7–10^9 autologous bone marrow mononuclear cells used for intracavernous injection. All subjects reported improvements of a subjective hardness score, which was verified by Doppler ultrasound. No AEs were reported within 6 months [71]. Despite this encouraging data, doctors should interpret current data with caution. Phase II and phase III data have not been published. SC therapy should not be profit-driven, and should currently only be offered in the context of well-designed clinical trials, that have been approved by ethics committees [69].

A phase I clinical trial reported the safety of intracavernous injection of a naked DNA plasmid encoding for a subunit of the human smooth muscle Maxi-K channel in 11 patients with ED. There were no serious side effects, and plasmids could not be detected in the semen. Even though the patients receiving the highest doses reported sustained improvements in erectile function over the 24 weeks study duration, no conclusions on efficacy could be drawn [72]. The same gene transfer, MaxiK, was tested in eight male monkeys with ED secondary to severe diet-induced atherosclerosis. Two weeks following injection, sexual behaviour was observed in the presence of estrogen-implanted females. The authors reported a two- to three-fold increase of erection duration [73].

50.5 Outlook on Potential Future Treatment Options in Neurogenic Bladder

In a pre-clinical rodent model postoperative neurogenic bladder dysfunction was induced by mechanical destruction of the bladder branch of the pelvic plexus (BBPP). Directly following the injury, cells were transplanted around the BBPP. Rats received either muscle-derived multipotent stem cells (Sk-34 and Sk-DN) or $CD45^+$ control cells. Four weeks following injury and cell transplantation animals were assessed functionally using urodynamic measurements and immunohistochemically. Pre-operative intravesical pressure was 7.9–9.7 cmH_2O. Post-operative pressure was 2.2 cmH_2O in the control (n = 11) and 7.6 cmH_2O in the stem cell group (n = 8). Staining experiments suggest that the stem cells were incorporated into the damaged nerves, and differentiated into Schwann cells, perineural cells, vascular smooth muscle cells, pericytes, as well as fibroblasts [74].

In a rat model of cerebral ischemia induced bladder dysfunction, deterioration of bladder function 7 days following cerebral ischemia (characterized by an increase of voiding pressure and post-void residual volume) could be prevented by pre-ischemic infusion of umbilical cord blood $CD34^+$ cells [75]. A rat model of 6-hydroxydopamine induced Parkinson, via stereotactic injection of the toxin into the nigro-striatal pathway, was characterized urodynamically [76]. Injection of human amniotic fluid stem cells or bone marrow derived mesenchymal stem cells into the damaged brain region could temporarily restore bladder function (day

14), but those effects subsided over time (day 28). Based on straining experiments, the authors suggested a temporary paracrine effect of stem cells, leading to an improved survival of dopaminergic neurons [77].

In rodent models of bladder outflow obstruction (BOO) related bladder dysfunction transplanted stem cells were shown to reduce bladder fibrosis and restore function [78, 79]. Interestingly histological and functional improvement through stem cells in rodent BOO models was observed following local (into the bladder) as well as systemic (intravenous) injection [80]. Injection of stem cells seems to stimulate local endogenous stem cells in the bladder wall, and hence induce a cascade-like effective gain [81]. On a pre-clinical level beneficial effects of stem cell transplantation on bladder function were shown for ischemia induced bladder dysfunction [82], hyperlipidemia induced bladder dysfunction [83], as well as in diabetic bladder dysfunction [84].

Gene transfer of a nerve growth factor (NGF) as a sub-unit via replication defective herpes simplex viruses via injection into the bladder wall led to a seven- to nine-fold increase of NGF expression (as assessed via ELISA) in the bladder wall as well as in L6–S1 dorsal root ganglia. This effect was more pronounced 3 days following the infection, compared to 21 days after infection (two to threefold increase). The authors concluded that vector gene therapy might be a means to alter bladder sensory innervation [85]. Using the same herpes simplex vector, another group transferred the gamma-aminobutyric acid (GABA) synthesis enzyme into the bladder wall of rats with a spinal cord injury (SCI) induced detrusor overactivity (DO). Gene transfer was performed 1 week following spinalization. Three weeks following GABA synthesis enzyme gene transfer and 4 weeks following injury, the rats were evaluated by cystometry. In the treated group non-voiding contractions were reduced around 40% compared to control spinalized animals. L6–S1 dorsal root ganglia showed increased staining patterns for the GABA receptors [86]. Using a non replication-defective herpes simplex vector another group evaluated kynurenine aminotransferase II gene transfer in the same SCI-DO rat model. Kynurenine aminotransferase II catalyzes conversion of kynurenine into kynurenic acid, an antagonist of excitatory amino acid receptors. Three weeks following intervention, kynurenine aminotransferase II gene transfer led to a significant decrease of urethral closure pressure (−24%) and maximum voiding pressure (−30%) compared to non-treated animals.

Hodges et al. showed that in vitro smooth muscle cells (SMC) from patients with neurogenic bladder produce more collagen than SMC from normal patients (4.1 vs. 1.8 µg/mL, as assessed via PCR). Epigenetic therapy with the histone deacetylase inhibitor trichostatin A was able to reduce collagen levels of neurogenic SMCs to normal levels, with no effect on cell viability (trypan blue experiments). The authors suggested that epigenetic therapy might prevent bladder fibrosis in patients with neurogenic bladders [87].

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Part XVII

Management for Complications

Urinary Tract Infections Among Patients with Neurogenic Bladder

51

Aurélien Dinh, Jérôme Salomon, and Pierre Denys

Abstract

Urinary tract infections (UTIs) in patients with neurogenic bladder (NB) are a major public health issue due to their high incidence and major consequences. They are associated with high morbidity and healthcare utilization, with a major economic burden. Their physiopathology, especially immunological and neurological function, is poorly understood. Some risk factors for UTI among patients with neurological bladder have been established: indwelling catheter, urinary stasis, high bladder pressure, bladder stones. Their diagnosis is a major challenge as clinical signs are often nonspecific and poor. Microbiological data are of limited help and varied flora could be involved. A urinary sample should be analyzed in appropriate conditions before any antibiotic prescription. According to most guidelines a bacterial threshold $\geq 10^3$ CFU/mL associated with symptoms are acceptable to define UTI among NB population. The management of acute, symptomatic UTI is not evidence based. A management with a single agent and a short antibiotic treatment of 10 days or less seems as effective as 15 or 21 days. Antibiotic selection should be based on patient based resistance patterns and the spectrum should be as narrow as possible. Asymptomatic bacteriuria (ABU) should not be treated, to avoid the emergence of bacterial resistance. Regarding preventive measures, use of clean intermittent catheterization (CIC), intravesical botulinum toxin injection, cycling antibiotic prevention are effective. Bacterial interference is promising but, randomized controlled trials are needed. We provide a review of data available on neurogenic bladder UTI.

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51.1 Introduction

Neurogenic bladder (NB) can be caused by a large panel of neurologic diseases such as spinal cord injury (SCI), which is the most studied model, multiple sclerosis (MS), Parkinson's disease, cerebral palsy, and stroke for example [1].

A wide variety of urinary tract infections (UTIs) can occur during NB, from lower UTIs with no fever to urosepsis and septic shock, which can lead to the diagnosis of abscess, lithiasis or urinary obstruction.

Their main outcomes are urosepsis and death, but they can also lead to chronic renal failure and hemodialysis.

UTIs among NB patients are difficult to study, particularly due to their heterogeneous symptomatology.

However, they remain a major cause of morbi-mortality and healthcare consumption, despite important progress in their management [2, 3].

Therefore, prevention is a major goal, but few strategies are available, although UTIs remain the most frequent complications of NB.

A lot of effort should be given to better understand the physiopathology of UTI among NB, especially concerning how they occur or their recurrence, in order to optimize their diagnosis, prevention and treatment.

Urinary microbiota could play an important role in this approach.

51.2 Epidemiology

In the United States, about 250,000 persons are spinal cord injured and about 150,000 have cerebral palsy, multiple sclerosis or Parkinson's disease, potentially leading to neurogenic bladder [4, 5].

In France, the prevalence of SCI (tetra- and paraplegics) is around 100,000. There are 1–2 cases of spina bifida for 1000 births [6]. According to the HAS (French Health Authority), the incidence in France of traumatic SCI is about 1200 new cases per year (around 19.4 new cases per

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_51

million inhabitants) [6]. Accidents cause over 50% of spinal injuries.

For comparison, European data indicate an incidence of spinal injury of all etiologies from 10.4 to 29.7 per million inhabitants per year. In the United States, the incidence is estimated at 40 per million inhabitants (11,000 new cases per year) [6].

From a neuro-urological point of view, the management of patients with SCI has greatly improved in the recent years, with an increase in life expectancy. However, UTIs remain the first cause of morbidity and the second cause of mortality in this population [7, 8].

These patients frequently carry urinary bacteria. Indeed, they have the highest rate of asymptomatic bacteriuria (ABU) [9]. The prevalence of ABU in patients using intermittent catheterization is estimated at over 50% (23–89% depending on the study) [9]. SCI patients are the most at risk of sepsis of urinary origin, especially patients who have indwelling catheter [10].

UTIs are the most frequent infections in SCI population with an overall rate estimated at 2.5 per patient and per year [11, 12]. Moreover, in a large study on medical claims from 2002 to 2007 among neurogenic bladder patients with SCI and multiple sclerosis (MS), more than 31% of patients were diagnosed with UTI within 1 year of diagnosis and 21% required hospitalization for UTI [3].

In this first year, the mean length of hospitalization was 15.5 days [13].

In spina bifida population, UTI is the most common complaint at emergency room [14]. Moreover, according to a retrospective cohort on canadian veterans, UTIs represented 51.2% of the visits at the emergency room among SCI patients [15]. In Turkey, Unsal-Delialioglu et al. showed that, among febrile SCI patients hospitalized in rehabilitation unit, 70% suffered from UTI [16]. This event significantly prolonged their hospital stay [16].

In general population, UTIs account for up to 40% of nosocomial infections, most of them being catheter-related. They can cause bacteremia in 2–4% of patients, and have been associated with a mortality rate three times higher than in non-bacteriuric patients [17, 18].

Because of these recurrent infections, patients with NB have a higher morbidity and mortality [19]. Death attributed to urosepsis in SCI patients is higher than in the general population. In a recent mortality study of 147 veterans with SCI over a 12-year period, death due to UTI was the second cause after pneumonia [20].

51.3 Microbiology

Enterobacteriaceae are the most involved bacteria in UTIs. In general population, Escherichia coli, Klebsiella and *Proteus* species are the most common causative agents. In patients with NB, they are still the predominant organisms involved, but their frequency is lower and other microorganisms, usually nosocomial germs such as Pseudomonas aeruginosa (8–15%), *Acinetobacter* spp. (15%), Enterococcus spp. (6–12%), and *Staphylococcus* spp., have a higher incidence [21–25].

Also polymicrobial UTIs are frequent (up to 26%) comparatively to non NB UTIs [1].

51.4 Antimicrobial Exposition and MDRO

Bacterial resistance constitutes a major public health issue, particularly since resistance is constantly increasing and there is no new class of antibiotics under development at this time. This initially affected Cocci Gram positive bacteria, such as *Streptococcus* and *Staphylococcus* [26]. But currently there is an emergence of resistance in Gram negative bacteria, with resistance mechanisms mediated by plasmids (CTX M). These bacteria, which are responsible for UTIs, are resistant to most beta-lactams (extended spectrum beta-lactamase (ESBL)), often requiring the use of carbapenems, the last beta-lactams remaining effective. As a result, these multidrug-resistant organisms (MDROs) have spread into the community and patients may contract infections to these MDROs without having been in contact with any hospital-related setting.

Due to frequent hospitalizations and antimicrobial treatments, SCI patients have a higher incidence of MDRO carriage and infections [25, 27–29].

Although emergence of MDRO is a global crisis in general population, it seems that it is not currently rising in SCI population.

Indeed, a retrospective study conducted in a French university hospital described the epidemiology of MDROs during bloodstream infection (BSI) and identified associated risks of MDROs among patients with SCI [30]. Of the 318 BSIs included in the analysis, the most frequent primary site of infection was urinary tract infection (34.0%). MDROs were responsible for 41.8% of BSIs, and this prevalence was stable over 16 years. No significant associated factor for MDRO BSI could be identified concerning sociodemographic and clinical characteristics, primary site of infection and bacterial species in univariate and multivariate analyses. Interestingly, BSI involving MDROs was not associated with initial severity of sepsis compared with infection without MDROs (43.8% vs. 43.6%, respectively) and was not associated either with 30th-day mortality (6.2% vs. 9.0%, respectively).

In conclusion, the authors suggested that during BSI occurrence in an SCI population, MDROs are frequent but remain stable over the years, whereas it is increasing in the general population. This discordance may be due to the already high proportion of MDROs in this specific popula-

tion because of high antimicrobial exposure. Moreover, it is difficult to measure an increasing prevalence as it is already substantial [30]. Two studies among SCI patients noted that 50% of strains isolated in urinalysis were MDROs [21, 31]. In another recent study, 41.7% of strains were classified as ESBL positive, and 50% were resistant to fluoroquinolones [22].

51.5 Pathogenesis

Due to neurological impairment, there are some modifications of structure, physiology and local immunology in the bladder and vesico ureteral tract.

In NB patients, some uropathogens acquire the potential to be internalized in cells of the urothelium. They also adhere to the cell walls and provoke inflammation that can lead to infections [32]. Pathogen adherence is mediated through complex host-pathogen interactions, for instance Fim-H/uroplakin Ia or LPS/Toll like receptor bindings [32].

51.6 Physiopathology

Due to NB, there is a high intravesical pressure and bladder ischemia, which contribute to decreased inflammatory reaction and lower antibiotic delivery [33]. Thus, improvement of urodynamic parameters such as intravesical pressure could reduce prevalence of UTIs [4, 34].

Moreover, the absence of physiological voiding when a bladder sphincter dyssynergia is present, is a major cause of UTI as it induces a chronic urinary retention. Therefore, regular catheterization to empty the bladder is of most importance to fight against UTI in this population [35].

Also, high intravesical pressure can lead to vesico-ureteral reflux which is a risk factor for pyelonephritis [11, 33].

51.7 Innate Immunity

Due to the use of urinary catheters to void the bladder in NB, several natural mechanisms to fight UTIs are altered.

- The protective perineal microbiota is modified, especially vaginal microbiota. Commensal Lactobacilli are replaced by *Enterobacteriaceae* and potentially virulent pathogens [33].
- The glycosaminoglycan (GAG) protective layer of the urothelium is also disrupted due to chronic inflammation [36–38].
- The rate of immunoglobulins A, which are part of the local innate immunity [33] that prevent from bacteria adherence to the urothelium [39], is lower in patients with NB than in non-NB patients [40].
- In NB, the mechanism in which urothelial umbrella cells usually present a rapid apoptosis when infected to protect from UTI, is also altered, or even absent [33, 41, 42].
- Local over-inflammation of the bladder present during NB is a major risk factor for UTI [43].
- The pro-inflammatory signaling and leukocyte components are modified in NB and antimicrobial peptides are down-regulated [19, 43].

51.8 Bladder Management

In case of NB from various origins, catheterization can be use to void. But catheterization contributes to introduce enteric bacteria mostly via the catheter-mucosal interface and the development of biofilms [44, 45].

Furthermore, microbial adhesion is enhanced and bacteria enter directly in the bladder whom surface cells are altered [44]. This enables ABU and infection by uropathogens [46, 47].

Once in the bladder, bacteria can produce biofilms composed with microcolonies with slow metabolism [48].

Usual natural host defense, such as Tamm-Horsfall proteins and urinary salts, are then ineffective and become part of the biofilm's exopolysaccharide matrix [49]. Moreover, biofilm can lead to urinary lithiasis [50].

Thanks to biofilms, bacteria are resistant to antimicrobial agents as they become physically difficult to reach [44]. And, via quorum sensing, bacteria can exchange resistance mechanisms between them [48].

51.9 New Data on Pathogenesis

51.9.1 Microbiome and UTI

Thanks to new microbiological technology 16S rRNA gene (16S rDNA) sequencing and metaproteomics the exploration of urine microbiome is new way of research [51].

Fouts et al. performed a cross sectional study comparing the microbiome of healthy volunteers and of subjects at risk for ABU due to spinal cord injury-related neuropathic bladder. A total of 589,454 quality-filtered 16S rDNA sequence reads were processed through a NextGen 16S rDNA analysis pipeline. Urine microbiomes differed by normal bladder function vs. neurogenic bladder, gender, type of bladder catheter utilized and duration of neurogenic bladder.

A healthy urine microbiome is characterized by a preponderance of Lactobacillales in women and *Corynebacterium* in men. We can hypothetize that the flora of healthy volunteers is protective against UTI. Therefore the administration of normal urinary flora could be a novel way to prevent UTI in NB [51].

51.9.2 Experimental Models

There are several experimental mice models studies of UTI in neurogenic bladder, as their neurogenic bladder phenotype and their urodynamic profiles are similar to humans with SCI [52–54].

Risk factors for UTI among human are established, but causation as increased susceptibility to UTI during NB are still not explained.

In a SCI rat model, a decreased immunological response has been shown after injection of E. coli in comparison to control rats and a persistent inflammation after clearance of bacteria. This study showed that SCI rats were more susceptible to UTI (a lower inoculum of *E. coli* is necessary to attempt infection) and less able to control with inflammation the infection due to *E*. coli [19].

In another study, SCI rats exhibited a delayed clearance of infection and exaggerated inflammatory responses in bladder and kidneys [43].

Susceptibility to E. coli and chronic inflammation of the bladder have been demonstrated, in SCI rat model, but there is still research to do to fully understand the mechanisms of such modification of local response.

51.10 Diagnosis

Diagnosis of a symptomatic UTI in patients with NB is a challenge as ABU is common in these patients. Indeed, catheter-associated ABU should not be screened, except for pregnant women and before urological procedures [44].

Currently, no gold standard is available, often leading to antimicrobial treatment overuse or delay for effective treatment. The definitions of UTI vary between studies and different guidelines.

51.10.1 Microbiological Criteria

Usual tools to detect UTI, i.e. urine dipsticks and urine cultures, are of limited help for diagnosis [44].

Urine dipstick in patient with NB and suspected UTI may be of little help as negative nitrites are associated in 55% with a positive urine culture [55]. So urine dipstick is not recommended in this case.

Therefore, in patients with NB, priority should be given to urine culture, and a urinalysis with complete susceptibility testing is of paramount importance.

However, the method to collect the sample should be precise and formalized for a correct interpretation of the result. The voiding method should be preferred [8, 56].

According to the Infectious Diseases Society of America (IDSA) guidelines for catheter-associated UTIs (CA-UTIs), patients with indwelling catheter should have their catheter removed prior to antibiotic therapy and then benefit from collection of a specimen following insertion of the new catheter [44]. Urine sample should never be collected from the drainage bag [44].

Standard definition for bacteriuria does not exist to the best of our knowledge. The IDSA provided some guidelines and stated that CA-UTI could be defined among patients with indwelling catheter, supra pubic catheter or intermittent catheterization by the presence of symptoms and a bacteriuria $\geq 10^3$ CFU/mL of at least 1 bacteria [44]. But for clinical research, they recommended a 10^5 CFU/mL threshold to optimize specificity [44].

The National Institute on Disability and Rehabilitation Research (NIDRR) recommended in 1994 to use a threshold of 10^2 CFU/mL for patients in intermittent catheterization and 10^4 CFU/mL for patients with condom catheter [57].

A recent systematic review found out that a bacteriuria $\geq 10^2$ CFU/mL was a reasonable threshold for patients with intermittent catheterization [58].

Nevertheless, whatever the chosen significant threshold, the clinical signs should always prevail [44].

51.10.2 Clinical Criteria

Symptoms of UTI among patients with neurological disease are poor and often aspecific. They also depend on the underlying neurologic disease.

The IDSA provided clinical practice guidelines in 2010 for catheter-associated UTIs, but NB was not specifically discussed [44].

Accordingly, pyuria is not a positive criteria for UTI [44] but the absence of pyuria has a high negative predictive value as illustrated by a recent review [58].

Other symptoms could be related to vesico-ureteral disorder: pollakiuria, urinal leak, urgency for catheterization, cloudy and malodorous urine, incontinence, back pain and bladder pain.

Some signs could be extra urinary, such as headache, sweat, high blood pressure, spasticity, malaise, lethargy and autonomic dysreflexia. These signs are nonspecific but could be linked and sometimes isolated during UTIs [59].

Fever is a severity sign that indicates urinal parenchyma impairment, which is at risk of sepsis.

In a prospective study, fever and autonomic dysreflexia were the more specific signs of UTI but had low sensitivity [60].

Linsemeyer et al. showed that 32% of SCI patients falsely believed they had a UTI while having a negative urine culture [61]. This study reinforced the necessity of a complete clinical evaluation before prescribing antibiotics in order to eliminate other causes such as fecal impaction, pressure ulcer.

It seems that NB patients better predict that they are free of UTI than they have a UTI [60].

The most prevalent signs according to a prospective study comparing symptomatic versus non symptomatic UTIs in male patients with SCI are cloudy and malodorous urine, and urinary incontinence [62]. Fever and high spasticity are less sensitive signs. Moreover, one third of the patients experienced only one sign, as one third experienced two signs, and the last third three signs.

Also, in the same study, quantitative bacteriuria and leucocyturia could not help for UTI diagnosis as, when performing ROC curves, no threshold could be determined with good sensitivity and specificity [62].

An International Spinal Cord Injury (SCI) Urinary Tract Infection (UTI) Basic Data Set presenting a standardized format for the collection and reporting information on UTIs in daily practice or research is freely available. It has been reviewed and approved by the Executive Committee of the International SCI Standards and Data Sets, and by the International Spinal Cord Society (ISCoS) Scientific Committee and the American Spinal Injury Association (ASIA) Board [59].

51.10.3 Cystoscopy

Cystoscopy is not of interest for systematic evaluation of UTI among patients with NB [63]. But in case of recurrent infections or obstructive infection, cystoscopy should be performed to identify urinary lithiasis, or local abnormalities such as diverticulae.

Annual exams with urodynamic tests are highly recommended as it has been shown that elevated bladder pressures are associated with UTI and deterioration of the upper urinary tract [11, 33, 64]. Ultra sound should also be performed at least annually for detection of lithiasis and hydronephrosis [58].

In conclusion, symptoms, biological signs and urinalysis are not very useful for UTI diagnosis. Nonetheless, in clinical practice, the presence of positive urine culture is of most importance, and its presence associated with clinical symptoms of UTI and no argument for other source of infection are sufficient to establish UTI diagnosis. Most of all, when antimicrobial treatment is prescribed, a reevaluation is necessary to adapt treatment and discuss about differential diagnosis if the clinical evolution is not favourable.

51.11 Treatment

Symptomatic UTI among patients with NB should always be treated as if they could be severe or lead to septic shock. Symptomatic UTI should be treated with the most specific and narrow spectrum antibiotics available for the shortest possible time [11].

Yet we should differentiate febrile UTI to non-febrile UTI.

Non-febrile UTIs are not urgent to treat, and waiting for urinalysis and susceptibility results is preferable before starting any targeted antimicrobial treatment. According to French guidelines, if empiric antimicrobial treatment should be started, nitrofurantoin is the preferred molecule, as there is few associated resistance and urine elimination, and it does not alter bowel or vaginal flora.

During febrile UTI, prescription of antimicrobial should be rapid to prevent acute sepsis and is mostly probabilistic. According to NIDDR, fever is the best marker of parenchymental lesion. Fever during UTI suggests the presence of tissue inflammation, which could lead to severe sepsis [65]. Fever in patients with infected urine is usually regarded as the most objective and specific indicator of upper tract involvement [66, 67].

Due to the high prevalence of bacterial resistance in the NB population, the choice of empirical antimicrobial treatment is challenging. Previous urine cultures and prior antimicrobial prescriptions should be considered, as well as the patient's intolerance or allergy. Moreover, ecology of the medical ward in case of health care infection should be taken into account.

Complete urine culture should be obtained prior to any antibiotic treatment [44], which is highly important as pathogens involved are often drug-resistant.

At first, parenteral beta lactam is the preferred choice, though an oral switch should be done when possible. Broad spectrum molecule is often necessary in case of MDRO.

The treatment should be reevaluated depending on the urinalysis result and the patient clinical course. Choice of the definitive antimicrobial drug should be with the narrowest spectrum possible and good bioavailability and urinal diffusion.

Fluoroquinolones are a dilemma as they have effective urine diffusion and 100% bioavailability, but also have a high potential selection of bacterial resistance.

Regarding treatment duration, it should be as short as possible. Overall, the use of antibiotics is characterized by a strong trend towards the reduction of treatment durations, which is well exemplified by the case of acute pyelonephritis, for which the usual treatment duration was 42 days in the 50s, whereas there are currently randomized controlled trials underway evaluating 5 days of treatment [68, 69]. In other infectious diseases, there is also a tendency to drastically decrease antibiotic treatment durations without adversely impacting efficacy.

A short course of 7 days for patients with prompt clinical response and 10–14 days for patient with delayed response is sufficient considering CA-UTI according to IDSA [11].

Darouiche et al. performed a non-inferiority clinical trial with a small sample size of 55 patients. They compared 5 days of antibiotic treatment associated with catheter exchange versus 10 days of antibiotic treatment without catheter exchange [70]. They found no significant difference regarding clinical cure.

In another trial, Dow et al. compared 3 days versus 14 days of ciprofloxacin (250 mg bid) in 60 SCI patients [7]. Microbiological cure was significantly better in the long treatment duration group. Nevertheless, some patients were infected with Enterococci resistant to ciprofloxacin, and the population was heterogeneous mixing febrile and non-febrile UTIs.

As a short treatment duration of 3 days seems to be insufficient, we could hypothesize that a 7-day treatment is enough for febrile UTI.

In our center, we treat febrile UTIs with 7–8 days of treatment when there is a prompt response.

In our opinion, UTI among NB needs to be managed as non NB when the bladder is stabilized and the antibiotic treatment microbiologically effective.

Therefore, the best indicator for treatment duration is clinical response.

In a retrospective cohort of febrile UTI among patients with NB, conducted from January the 1st 2008 to December the 31st 2013 in a French university hospital, Dinh et al. studied antibiotic treatment duration [71].

One hundred and fifteen episodes occurring among 96 patients were divided into three groups according to antibiotic treatment duration (<10 days, between 10 and 15 days, and >15 days). The cure rates were not significantly different (71.4%, 54.2%, and 57.1%, respectively; $p = 0.34$). Moreover, there was no difference in cure rate between mono and dual therapy (44% for monotherapy versus 40% for dual therapy; $p = 0.71$) [71].

In their cohort study among 318 BSI episodes in SCI patients, Saliba et al. showed that UTI were treated with a global mean treatment duration of 18.70 ± 11.14 days with a mean dual therapy of 6.97 ± 9.99 days [72].

Also, when focusing on signs of severity (volume expansion, assisted (mechanical) ventilation, vasopressor requirement or intensive care unit admission) during these BSI episodes associated with UTI, their prevalence was 31.5% [72].

In these data, the mortality rate was low (1.9%). Several hypotheses could be suggested to explain this situation: the generally younger age of the SCI population, their lack of underlying illness, and the possibility of a particular immunity due to recurrent infections such as UTI and the development of antibodies against bacteremia [73–75] .

The IDSA guidelines on CA-UTI recommend a 5-day treatment with levofloxacin if the bacteria is sensitive and if there is a rapid clinical response [44]. In our opinion, fluoroquinolones should be spared to prevent from bacterial resistance. Thus, trimethoprim/sulfamethoxazole could be a good alternative, with a good bioavailability and excellent urinary diffusion.

Fosfomycin also has attractive characteristics: it has a good activity against biofilm, particularly when associated with aminoglycosides and fluoroquinolones [76–78]; it could be administered in single dose with long term activity with mainly urinary excretion [76]; its spectrum is broad (ESBL gram negative bacteria, methicillin-resistant *Staphylococcus aureus*) [79]; dose does not need to be adapted to renal or liver function [76]; and diffusion in prostatic tissue is excellent [80].

However, no evidence of its efficacy in NB is available despite its wide use.

To conclude, antibiotic stewardship should be optimized as the prevalence of MDRO is high in this specific population [30].

ABU should not be treated, especially among NB patients. Thus, it should not be tested, and no urine culture should be performed.

Indeed, the treatment of ABU does not prevent from febrile UTI or recurrence of infection, and contributes to an increase of bacterial resistance and toxicity due to antibiotic [5, 11, 44].

Moreover, treating ABU seems to lead to symptomatic UTI [81].

There are two exceptions: pregnancy and urological procedure with potential urethral bleeding [44].

51.12 Prevention

51.12.1 Catheter–Related Measures

51.12.1.1 Closed Catheter Drainage

One of the most important prevention of UTI for patients with indwelling catheters is the use of closed catheter drainage system [44].

Moreover the drainage bag should be below the bladder [44].

Concerning the change of the indwelling urinary catheter it is now recommended not to change it systematically but only in case of obstruction, hematuria or UTI [9].

51.12.1.2 Method of Bladder Management

Intermittent catheterization is associated with fewer UTI than other methods [11, 44].

Concerning the choice of catheter a recent meta-analysis did not find any benefit to hydrophilic-coated catheter compared to uncoated catheter use [82].

Impregnated catheters with antibiotic or silver-coated catheters have shown impact on bacteriuria and infection but only in the very short term [64, 82]. But antibiotic resistance and silver toxicity have been notified after long-term use [64].

51.12.1.3 Other Measures

Use of antimicrobials or antiseptics in the urinary drainage bag is not recommended due to their absence of effect [83].

Moreover catheter irrigation with antimicrobials or normal saline is not efficient and could be deleterious [84].

51.12.2 Medical Measures

51.12.2.1 Antibiotic Prophylaxis

The effectiveness of antibiotic prophylaxis for UTI is under debate among patients with neurogenic bladder.

Two meta-analyses did not support the use of daily antibiotic prophylaxis for the prevention of symptomatic UTI in NB patients and support the rising incidence of antimicrobial resistance [85, 86].

Anyway the overall quality of these studies was low and they included several methods of bladder drainage, as mixed male and female patients [86–88].

Therefore, daily antibiotic prophylaxis is not recommended for the prevention of UTI in NB patients [88].

One before-after study evaluated the impact of weekly oral cycling antibiotics in SCI patients with CIC and stabilized bladder. Antimicrobials were chosen according to their urinary flora. A significant reduction of UTI and MDRO carriage was observed [89]. The same team studied this strategy in a more heterogeneous population with multiple sclerosis, brain damage, stroke with different type of bladder management indwelling catheter, condom drainage as CIC and IC. They confirmed the efficiency of the strategy. Moreover they also confirmed the absence of emergence of bacterial resistance during a long follow-up (mean: 5.25 years) [90].

51.12.2.2 Cranberry Prophylaxis

Currently literature does not show evidence of positive effects of Cranberry to prevent from UTI in a NB population [44, 91]. One prospective, double-blinded, placebo-controlled, crossover study failed to find statistically significant favorable effect for cranberry among 21 patients with NB [92].

Only a small randomized study vs. placebo found a significant reduction in the incidence of UTI with cranberry prophylaxis in the NB population [93].

J. P. Lavigne et al. performed a randomized, cross-over human trial including five volunteers who followed six different regimens with or without variable doses of cranberry and propolis.

They concluded that propolis had an additional effect with cranberry and prevented from bacterial adhesion [94].

51.12.2.3 Methenamine Salt Prophylaxis

Methenamine did not prove any significant effect on UTI during neurogenic bladder in a meta analysis [44]. Thus it is not recommended.

51.12.3 Procedural Interventions

51.12.3.1 Intravesical Botulinum Toxin A

Injection of intravesical botulinum toxin has demonstrated positive effects on neurogenic detrusor activity. It improves urodynamic parameter as continence of patients in several studies [95].

Some data seem to show that they also have a positive effect on prevention of UTI [96].

Overdistention of the bladder may also result in poor blood supply, which is a risk factor for UTI [33].

51.12.3.2 Bacterial Interference

Bacterial interference is a promising non antibiotic way to fight UTI among patients with neurogenic bladder. The principle is to introduce a non pathogenic strain of E. coli in the bladder of patients suffering from recurrent UTI. This strain competes with natural pathogenic strain and struggles for nutriment as adhesion. Once the patient is colonized with non pathogenic strain, UTI become rare.

Currently two strains of Escherichia coli are available: one with natural deletion of the pili and one with "technical deletion" of pili. Seven studies have been performed on patients with neurogenic bladder.

In one multicenter non randomized controlled trial, Darrouiche et al. compared the effectiveness of bacterial interference versus placebo in preventing urinary tract infection. Adult patients with neurogenic bladder after spinal cord injury and a history of recurrent UTI could be included. Sixty-five patients have been randomized to receive either *Escherichia coli* HU2117 or sterile saline. Patients were evaluable if they remained colonized with *E. coli* HU2117 for >4 weeks. Finally, 27 patients were evaluable (17 in the experimental group and 10 in the placebo group). The average number of episodes of UTI/patient-year in the experimental group was lower (P = 0.02, Wilcoxon rank sum test) (0.50) than in the control group (1.68) [97].

In another prospective clinical trial, adult inpatients with spinal cord injury (SCI) (>1 year) with neurogenic bladder that required indwelling (transurethral or suprapubic) catheter drainage and who had had at least one clinically recognized UTI in the past were enrolled. After completion of antibiotic therapy, a urinary catheter that had been incubated in broth with E. coli HU2117 for 48 h was inserted and then removed after 28 days. Ten of 12 subjects were successfully colonized for 14 days or more. The rate of symptomatic UTI during ABU was 0.15 per 100 patient-days (1 case) [98].

Others studies also shown efficacy of this strategy [92, 99–101].

The main limit is the difficulty to obtain ABU with the non pathogenic strain which requires sometimes several inoculation sessions.

51.12.3.3 Vaccination

Vaccination with *E. coli* by oral route has shown efficacy to prevent from UTI in non neurogenic bladder population [94, 102, 103]. Nevertheless its effect is suspensive and the procedure is burdensome.

No data are available for patients with neurogenic bladder despite it could be another means to prevent UTI.

51.12.3.4 Sacral Neuromodulation

Sacral neuromodulation is used for detrusor overactivity. In one study it has shown an efficacy against UTI [104].

51.12.4 Prevention of Infection During Urologic Procedure

The prevention of urinary infections and the preservation of the upper urinary tract is essential in this population. Bladder-sphincter balance must be monitored by regular urodynamic assessments (UDA). It is recommended to carry out UDA at least twice-yearly during the first 2 years, then annually depending on the urodynamic risk factors of the patient (high endovesical pressure, method of voiding) and the level of the neurological lesion [105].

The role of antibiotic for prevention of UTI is unclear.

Prophylactic urinary antibiotics are recommended for invasive urological procedures with a risk of hematuria such as transurethral resection of the prostate and prostate biopsies [106, 107].

But no randomized control trial concerning UDA is available to this day to the best of our knowledge. In an era of ever increasing microbial resistance, data are urgently needed to avoid unnecessary antimicrobial exposure.

51.13 Conclusions

UTIs are a major issue for patients with neurogenic bladder, as they are frequent and difficult to treat with a high prevalence of MDRO involved. Moreover they have a high rate of recurrence and their diagnosis is still a challenge.

Many more data on this subject are needed, especially concerning their diagnosis, physiopathology, risk factors for recurrence, optimal antibiotic treatments and non-antibiotic prevention methods.

Randomized control trials should be performed.

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Vesico-ureteral Reflux

52

Jürgen Pannek

Vesico-ureteral reflux (VUR) in patients with neurogenic lower urinary tract dysfunction (NLUTD) can either be due to reasons unrelated to NLUTD, like morphologic changes, or can develop as a secondary complication of NLUTD, e.g. due to elevated pressures during storage and/or voiding, or due to bladder wall fibrosis. Cystography remains the gold standard for diagnosis of vesico-renal reflux. The most commonly used grading system distinguishes lower grade reflux (reflux grade I = does not reach the renal pelvis, grade II = reaches the renal pelvis, but no dilatation; grade III = mild dilatation of the collecting system, normal/minimally deformed fornices) from higher grade reflux (grade IV = moderate dilatation of the collecting system, blunt fornices; grade V = marked dilatation of the collecting system/hydronephrosis) [1].

High grade VUR is regarded as a risk factor for recurrent pyelonephritis and reflux nephropathy pyelonephritis and renal scarring [2]. Therefore, correction of VUR should be considered in patients with NLUTD.

If the VUR is caused by elevated detrusor pressure during the storage phase (secondary reflux), initial treatment consists of treatment of neurogenic detrusor overactivity (NDO). It has been demonstrated that effective treatment of NDO, e.g. by onabotulinum toxin injection in the detrusor, VUR can be treated effectively [3]. In addition, it has been demonstrated that onabotulinum toxin injections, even if they include the trigone, do not cause VUR [4].

If reflux persists despite adequate suppression of NDO, endoscopic treatment is regarded as first choice therapy, but data about the outcome of this intervention in patients with NLUTD are scarce. Short- to mid-term success rates of approximately 60% are described [5], whereas long-term outcome is less favorable, with success rates of 25% [6]. Not surprisingly, high-grade reflux and persistent NDO are correlated with treatment failure [7]. The most frequently used substance for endoscopic VUR treatment today is dextranomer/hyaluronic copolymer, with proven efficacy and low complication rates [8].

Given the low complication rate of this minimally invasive procedure, endoscopic treatment of VUR should be considered as first-line treatment in primary as well as in secondary low grade VUR, in the latter after treatment of NDO, even if there is a substantial risk that re-interventions are required.

If conservative or minimally invasive treatment is not sufficient to treat NDO, bladder augmentation may be required. If NDO is combined with VUR, the question arises if VUR should be treated surgically during the same procedure. The existing data demonstrate that over all, low-grade VUR resolves in about 90% of the patients, whereas high-grade reflux persists in about 50% of the patients [9]. Therefore, simultaneous anti-reflux surgery should be considered predominantly in patients with high-grade reflux, but not in those with low-grade VUR [9]. Unfortunately, virtually no data exist concerning the best surgical technique for antireflux surgery. Therefore, the technique should be based on the anatomical situation (e.g. bladder wall/ureter thickness) and the personal experience of the surgeon.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_52

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Upper Urinary Tract Dilation

53

Limin Liao

Neurogenic bladder (NB) refers to lower urinary tract (LUT) dysfunction caused by various nervous system diseases. High bladder pressure is a serious problem, and can be transmitted to the upper urinary tract (UUT), resulting in hydronephrosis (HN) and ureteral dilation (UD), which are called as upper urinary tract dilation (UUTD). Ureteral obstruction at the bladder wall is another reason of UUTD, but is less of a concern in previous publications. UUT dilation or deterioration could result in chronic renal failure. Therefore, evaluation and protection of UUT function are extremely crucial in the management for NB [1, 2].

The most common method by which to detect HN and UD is ultrasonography (US). HN is subjectively graded as mild, moderate and severe. In 1993, The Society for Fetal Urology (SFU) described an US grading system based on renal sinus splitting patterns and dilation of the renal pelvis and calyces [3]. The SFU grading system is widely accepted, but is not popular among clinical urologists. The deficiencies have been identified [4, 5]. Other investigators have suggested improvements for it [4–7]. Moreover, US findings are not easy to interpret because the kidneys and ureters are not shown in the same image, and assessment of UUTD is somewhat subjective. In this chapter, a grading system for UUTD (HN and UD) based on magnetic resonance urography (MRU) is described, and attempt to provide a more objective, intuitive and understandable method for UUTD grading. The applications of the MRU-UUTD grading system and a comprehensive classification system for both LUT and UUT dysfunction in patients with NB are also described.

53.1 MRU-UUTD Grading System

The MRU-UUTD was graded via a developed grading system that was reported by Liao [8, 9]. The MRU-UUTD grading system is based on MRU findings, is systematically described in detail, and corresponds to the SFU and Onen grading systems based on US findings [3, 4]. It is derived from the MRU coronal and transverse image panel, and the maximum intensity projection MRU is as follows:

1. Grade 0: The central renal complex is closely apposed without any separation and the ureteral dilation from the coronal and transverse MRU images and the maximum intensity projection MRU (Fig. 53.1).
2. Grade 1: There is slight separation of the central renal complex, but no visualized calices; the ureter is <7 mm from the coronal and transverse MRU images and the maximum intensity projection MRU (Fig. 53.2).
3. Grade 2: The renal pelvis is dilated, and one or more calices may be visualized, but the renal parenchyma over the calices is normal; the ureter is <10 mm from the coronal and transverse MRU images and the maximum intensity projection MRU (Fig. 53.3).
4. Grade 3: The renal pelvis is further dilated and there are fluid-filled calices throughout the kidney. The renal parenchyma over the calices is beginning to thin, but the renal parenchyma loss is <50%. The ureter is tortuous and <15 mm from the coronal and transverse MRU images and the maximum intensity projection MRU (Fig. 53.4).
5. Grade 4: As in grade 3; however, the renal parenchyma is significantly thinned (renal parenchyma loss >50%). The ureter is severely tortuous and >15 mm from the coronal and transverse MRU images and the maximum intensity projection MRU (Fig. 53.5).

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_53

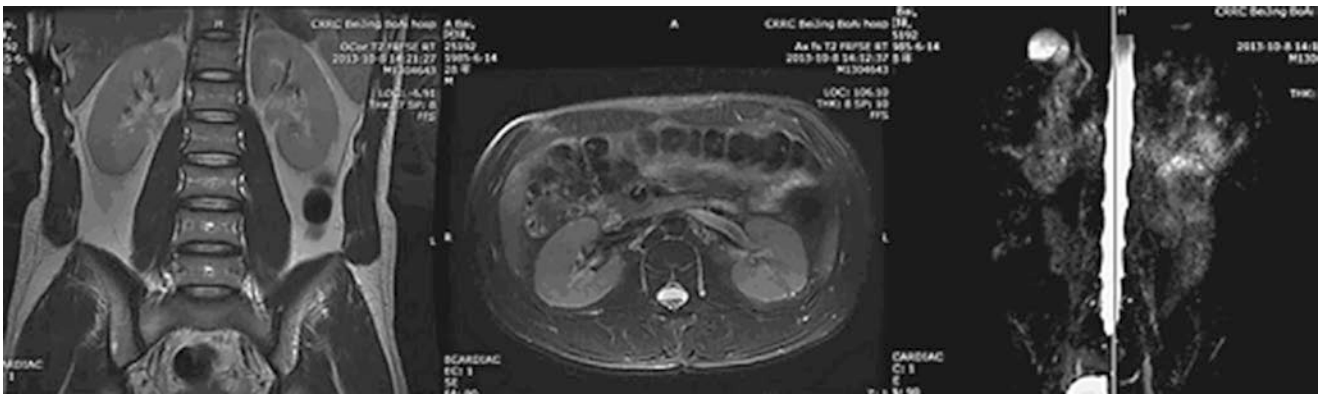

Fig. 53.1 MRU-UUTD grading system: Grade 0, normal

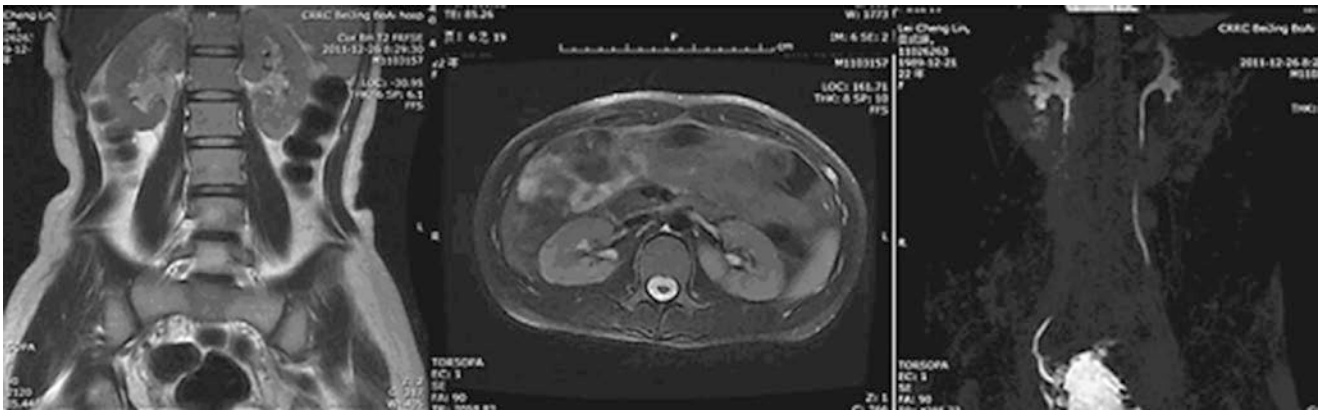

Fig. 53.2 MRU-UUTD grading system: Grade 1

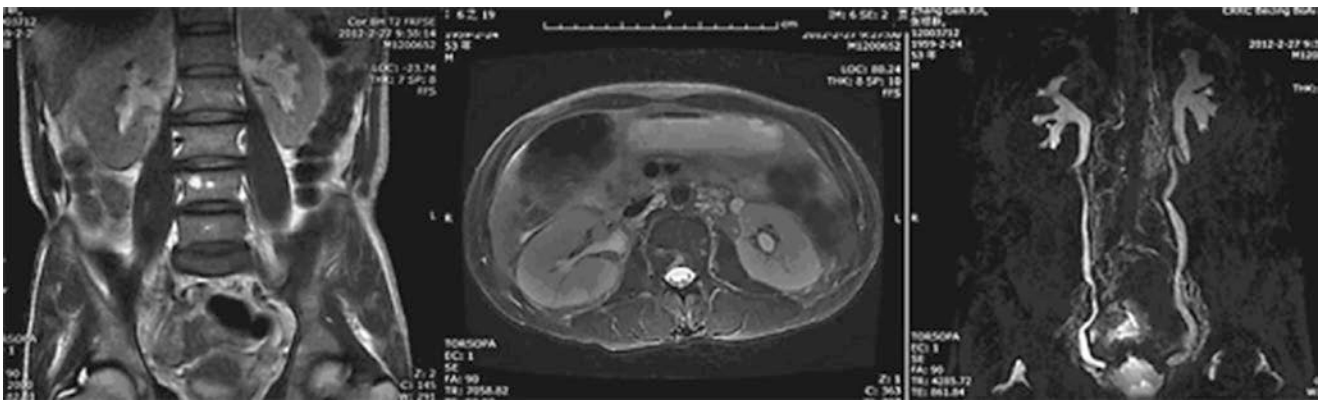

Fig. 53.3 MRU-UUTD grading system: Grade 2

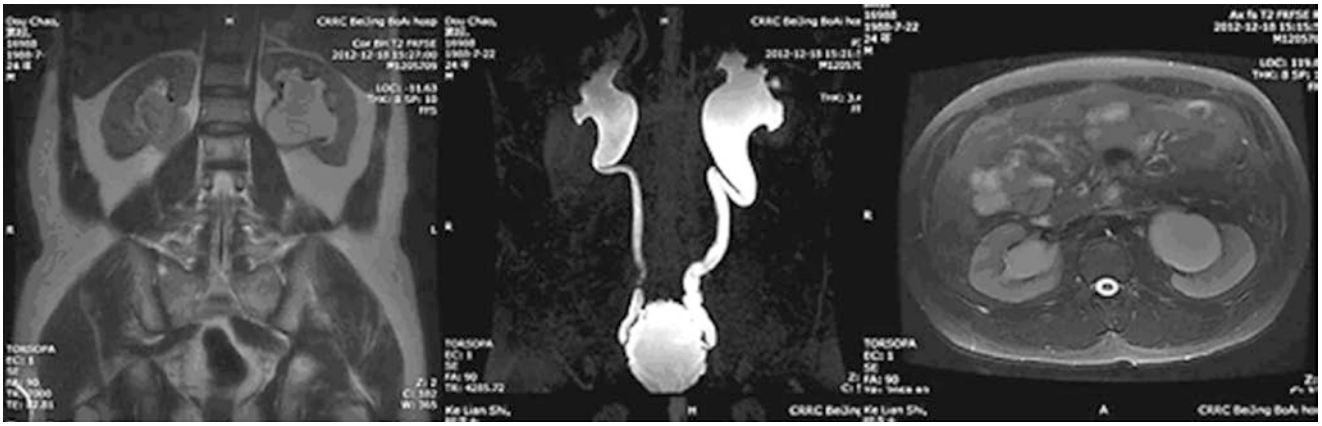

Fig. 53.4 MRU-UUTD grading system: Grade 3

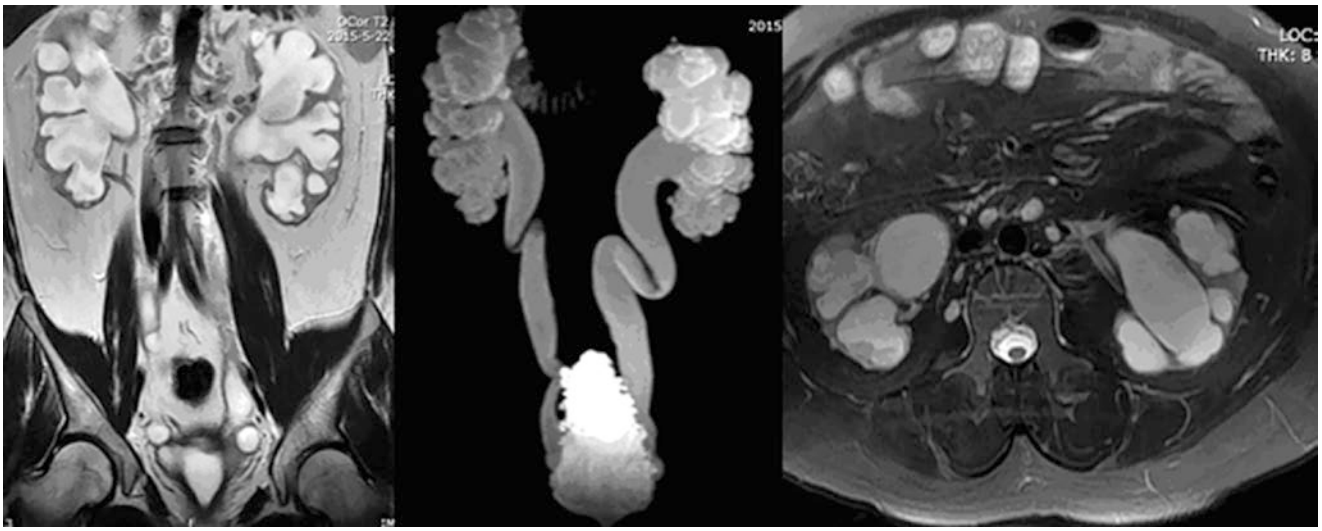

Fig. 53.5 MRU-UUTD grading system: Grade 4

53.2 Evaluation of UUT Function

HN is most commonly classified as mild, moderate and severe by renal US. To correlate the MRU-grading system with the SFU system, SFU-HN grades and MRU-UUTD grades were compared among 70 patients with unilateral or bilateral UUTD at our center. The results showed that 70 patients had a total of 95 sides with UUTD. There was no significant difference in the distribution of grades between the MRU-UUTD and US-HN grading systems ($p > 0.05$), but there was a significant difference in grades 3 and 4 between the two systems ($p < 0.05$). The MRU-UUTD grade correlated well with the SFU-HN grade. According to the SFU system, 5.3% of patients with UUTD were changed from grade 4 to grade 3 according to the MRU-UUTD system.

Evaluation of UUT function is the first step in achieving the goal of protection of UUT function. The main paradigm for describing and grading HN is US-SFU grading system. The appearance of the calyces, dilation of the renal pelvis, and thinning of the renal parenchyma are keys in determining the SFU-HN grades. HN and renal parenchymal thickness have an inverse relationship: kidneys with more significant HN have less renal parenchyma. Because renal parenchyma loss is a lengthy, gradual, pathologic process, some kidneys with moderate HN demonstrate the onset of renal parenchyma thinning. In MRU-UUTD system, mild or moderate renal parenchyma loss was added to the definition of grade 3. To date, MRI remains an attractive imaging modality because of the absence of radiation exposure and superior resolution when compared to US. The MRU is

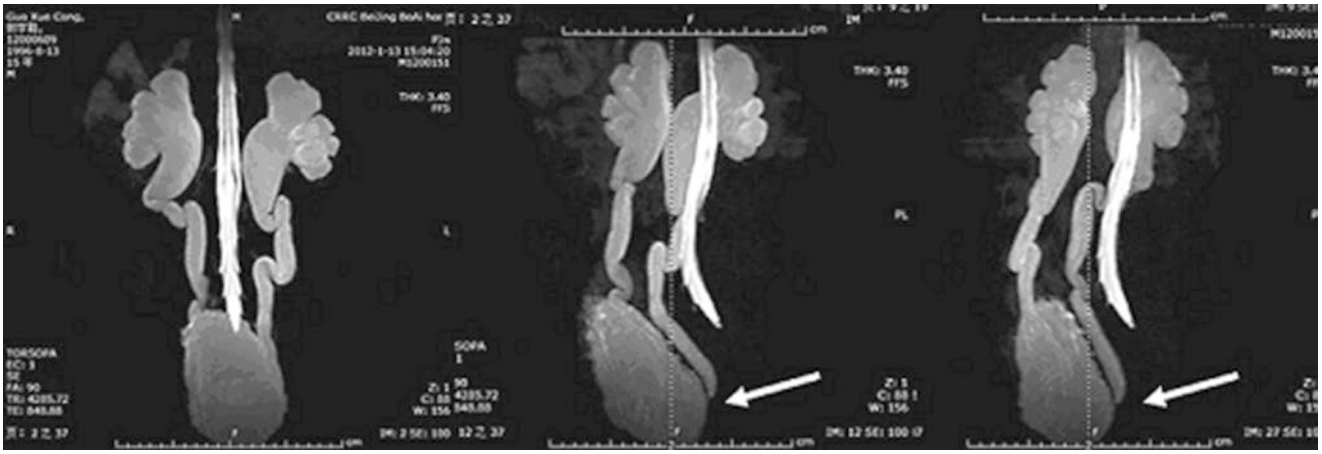

Fig. 53.6 Distal ureteral obstruction: HN and UD can be displayed during 360° rotation, and vesicoureteral junction stricture or obstruction can be clearly shown (arrows: left and right ureters)

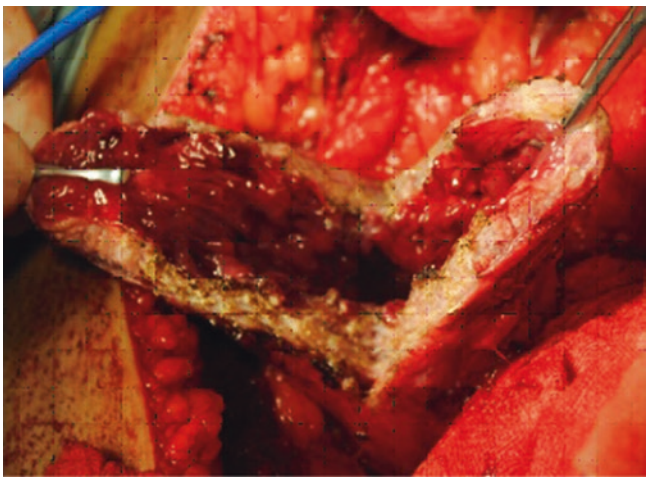

Fig. 53.7 Fibrosis and thickening of the detrusor in a neurogenic bladder patient

easy to use and understand by a clinical urologist and can objectively and simultaneously show all images of the kidney and ureters from different panels. The MRU-UUTD grading system described the MUR images of each grade from different panels, and correlated well with the US-SFU grades. This MUR grading also emphasizes the lengthy, gradual thinning process of the renal parenchyma, narrows the span between grade 3 and 4, and is more reasonable. The US-SFU grading system lacks clarity and depends heavily on individual interpretation from the US examiner. The value of the MRU-UUTD system is that the subjective factor of visual interpretation is reduced for one observer over time, as are discrepancies between multiple observers. In place of the MRU-UUTD system, a more objective interpretation for UUTD is generated. Another advantage is that HN and UD can be observed completely and described from the coronal and transverse panel MRU and the maximum intensity projection (MIP) MRU. The HN and UD can be displayed in the same image of the MIP-MRU during a 360° rotation, and the vesicoureteral junction stricture/obstruction (UVJS/UVJO) can be clearly shown (Fig. 53.6).

For patients with NB, the morphology and innervation of the ureterovesical junction (UVJ) play an important role in the occurrence of vesicoureteral reflux (VUR) and UD. NB of long duration and irregular bladder management may result in the high percentages of HN, UD, VUR, and UUTD or UUT deterioration. Most of patients at our center had moderate-to-severe HN and UUTD or UUT deterioration at the first evaluation. In these patients, detrusor fibrosis, detrusor thickening and decreased bladder compliance secondary to progressive destruction of the bladder wall (Fig. 53.7) often cause ureteral stricture within the bladder wall, distal ureteral obstruction and UUTD. UUTD is one of causes for the renal failure. The evaluation using this MRU-UUTD grading system is important in the management of NB patients before treatment, and can facilitate better informed clinical decision-making.

53.3 Classification for UUT Dysfunction

The existing classification schemes for LUT dysfunction have only focused on the bladder and urethra and do not relate to UUT dysfunction, including HN, VUR, and UD. Herein, a comprehensive classification system for both LUT and UUT dysfunction in patients with NB is suggested by Liao (Table 53.1) [10, 11]. The MRU-UUTD grading system was also used to establish this comprehensive classification system. In Table 53.1, LUT dysfunction is described according to the Guidelines of the European Association of Urology (EAU) and the terminology of the International Continence Society (ICS). VUR was graded according to the

Table 53.1 A comprehensive classification system for LUT and UUT dysfunction in patients with neurogenic bladder from Liao

Lower urinary tract		
Storage	Voiding	Upper urinary tract
Bladder function	**Bladder function**	**Vesico-ureteral reflux**
Detrusor activity	Detrusor contractility	No
Normal	Normal	Yes: Unilateral, bilateral
Overactive	Underactive	Degree (left, right)
	Acontractile	I
Bladder sensation		II
Normal	**Urethral function**	III
Increased or hypersensitive	Normal	IV
Reduced or hyposensitive	Functional Obstruction	V
Absent	Urethral overactivity	
	Detrusor external sphincter dyssynergia	**Upper urinary tract dilatation**: Hydronephrosis and ureteral dilatation
Bladder capacity	Detrusor bladder neck dyssynergia	No
Normal (300–500 mL/cm)[a]	Sphincter overactivity	Yes: Unilateral, bilateral
High (>500 mL)	Non-relaxing sphincter	Grade (left, right)
Low (<300 mL)	Non-relaxing bladder neck	1
	Mechanical obstruction	2
		3
Bladder compliance		4
Normal (20–40 mL/cmH_2O)		
High (>40 mL/cmH_2O)		**Ureteral obstruction in bladder wall**
Low (<20 mL/cmH_2O)		No
		Obstruction (left, right)
Urethral function		
Normal		**Renal function**
Sphincter acontractility Incompetent		Normal (**GRF** >50 mL/min, left, right)
Bladder neck		Renal insufficiency (GRF <50 mL/min, left, right)
External sphincter		Compensatory (GRF, left, right, Creatinine <1.5 mg/dL)
		Decompensation (GRF, left, right, Creatinine >1.5 mg/dL)

[a]For adults

International Reflux Study Group (IRSG) classification [12], and kidney function was determined by the glomerular filtration rate (GFR) from isotope renography and the serum creatinine level. UUTD was graded by MRU-UUTD system. This classification system better discriminates among grade changes in UUT function, can provide objective indicators for the urinary tract function, especially UUT function, and is an important means of long-term follow-up of conservative and surgical treatments.

53.4 Management for UUTD

Accordingly, the results of UUTD management may improve as well. The earlier correction for UUTD has been shown to yield better drainage from indwelling transurethral catheters. If the UUTD grade can be improved and the bladder condition is still poor, augmentation cystoplasty (AC) without ureteral re-implantation (UR) can be performed. If the UUTD grade could not be improved, augmentation cystoplasty (AC) with ureteral re-implantation (UR) should be performed; ureteric adhesiolysis and tailoring/shortening often are necessary in this situation. The renal parenchyma thickness is a predictor of renal function recovery [13]. Worsening HN and UD are relative indications for AC surgery; however, some, but not all UUTD grades are indications for AC. Specifically, grade 4 MRU-UUTD is not a legitimate indication for AC due to excessive renal parenchyma loss.

A patient with HN, UD, tortuous knotting, and UVJS/UVJO clearly needs MRU instead of a simple renal US. In cases in which only an US is done, the patient should not undergo ureteral tailoring/shortening and re-implantation during AC and renal function cannot be protected, especially in cases with ureteral obstruction due to ureteral tortuous knotting and absent UVJS/UVJO (Fig. 53.8).

The MRU-UUTD system can better discriminate the change in UUTD grades, provide an objective index for UUT function. It is an important parameter of long-term follow-up of conservative treatments and surgeries can be used for longitudinal monitoring of UUTD (HN and UD), including pre- and post-operative observation; an example of evaluation for the outcome of the AC operation is shown in Fig. 53.9.

53.5 Conclusion

UUTD is one of important complications in NB patients. The evaluation and management for UUTD is crucial for the prevention of chronic renal failure. Based on the MRU findings, the UUTD grading system was developed and

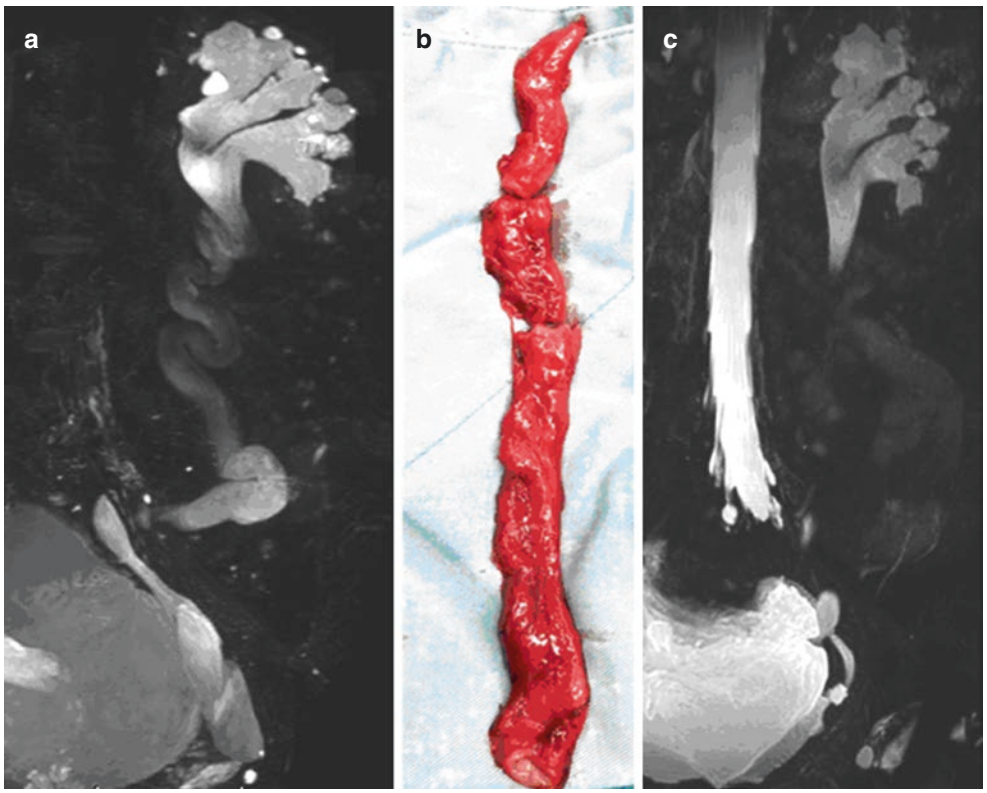

Fig. 53.8 MRU-UUTD grades before and after surgery in a patient with NB: (**a**) UVJO/UVJS may be related to VUR, ischemia, chronic inflammation, fibrosis, and thickening of the bladder wall. UVJO usually leads to hydronephrosis, ureteric dilatation, tortuosity, adhesions, and CFR. The sites of obstruction usually begin at the UVJS, and fibrotic cords always form at tortuous points. (**b**) Ureteral re-implantation (UR) with ureteric adhesiolysis and tailoring/shortening are necessary in the preceding condition. Hydronephrosis in the absence of VUR and UVJO results from ureter tortuosity and adhesions above the bladder wall; for these patients, AC alone does not improve UUT deterioration, and UR with ureterolysis and ureteric tailoring/shortening are usually combined with AC. (**c**) Three months after surgery, the MRU-UUTD grade improved significantly

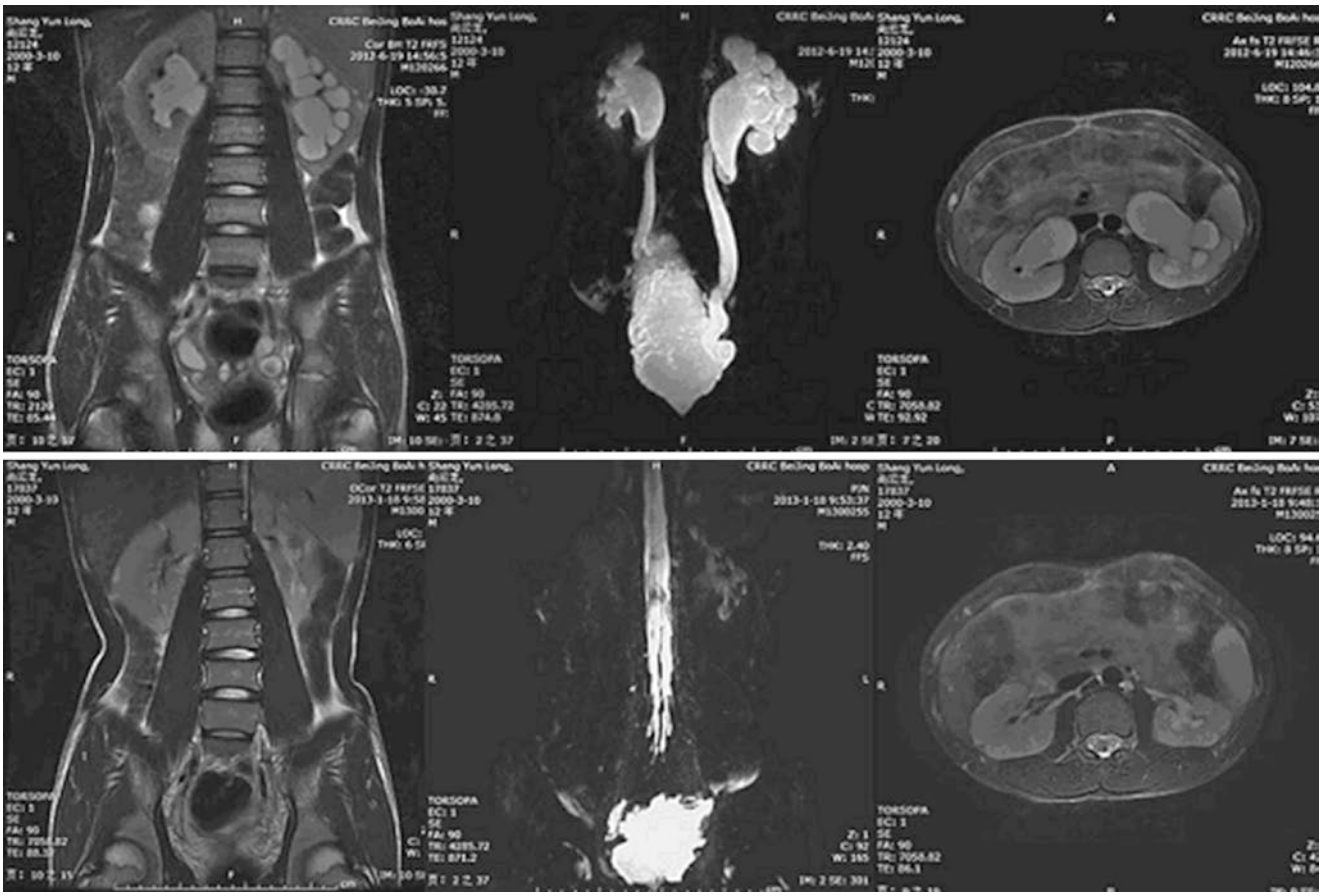

Fig. 53.9 Improvement of MRU-UUTD grades 6 months after augmentation enterocystoplasty. Upper: Pre-operative MRU-UUTD grades of right and left kidneys were 3 and 4, respectively. Lower: Post-operative MRU-UUTD grades of right and left kidneys were 0 and 1, respectively. A significant improvement is shown

described. Because MRU-UUTD grading system provides an objective and comprehensive evaluation for UUTD (HN and UD), it can be used to evaluate UUT function and for longitudinal monitoring of UUTD. It also allows for better informed clinical decision-making by identifying changes in the UUTD and using follow-up for treatment outcome.

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Bladder/Pelvic Pain and Neurogenic Inflammation

54

Lori Ann Birder

54.1 Overview

Bladder and/or pelvic pain is prominent in patients with chronic prostatitis as well as interstitial cystitis/bladder pain syndrome (IC/BPS). The etiology of IC/BPS remains elusive and may involve multiple causes. IC/BPS has often been described as a disease of the urothelium. Ultrastructurally, an altered vascular supply is observed in its ulcerative form with locations of moderate-to-severe redness, interspersed among a whitish discoloration. There is also evidence that the urothelium is associated with altered synthesis of a number of proteins including those involved in cellular differentiation, barrier function and bacterial defense mechanisms. In addition, neurogenic inflammation of the bladder mucosa may be present in a percentage of patients with IC/BPS in addition to those with prostatitis, chronic pelvic pain and spinal cord injury. The urothelium, which lines the inner surface of the renal pelvis, the ureters and the urinary bladder, not only forms a high-resistance barrier to ion, solute and water flux, and pathogens, but also functions as an integral part of a sensory web which receives, amplifies, and transmits information about its external milieu. Urothelial cells have the ability to sense changes in their extracellular environment, and respond to chemical, mechanical and thermal stimuli by releasing various factors such as ATP, nitric oxide and acetylcholine and impart these changes to underlying bladder nerves and the central nervous system. Changes in these signaling mechanisms associated with lower urinary tract symptoms are discussed as well as new areas for therapeutic interventions.

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54.2 Functional Anatomy

54.2.1 Mucosa

The bladder wall has three well-defined layers: the mucosa (innermost portion), the muscularispropria, and the adventitia/serosa. The mucosa (urothelium, basement membrane, lamina propria) also contains some smooth muscle cells, muscularis mucosae [1, 2] (Fig. 54.1).

54.2.2 Urothelium

The uroepithelium, or urothelium, lines the renal pelvis, ureters, bladder, upper urethra, and glandular ducts of the prostate and forms the interface between the urinary space and underlying vasculature, connective, nervous and muscular tissues [3]. The urothelium is a transitional epithelial tissue, composed of at least three layers: a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells known as umbrella cells. Tight junctions, localized between the superficial umbrella cells are composed of multiple proteins such as the occludins and claudins. These proteins, along with uroplakins, which are crystalline proteins that assemble into hexagonal plaques, contribute to the urothelial barrier function [4, 5]. The major part of the urinary tract shows similarity between a number of species and is lined with a fully differentiated urothelium. In contrast to the proximal urethra, there appears to be little difference between the urothelium of the trigone and the detrusor.

54.2.3 Lamina Propria

A focus of much of lower urinary tract (LUT) research has been afferent mechanisms and the processes of how afferent information is generated and conveyed to the central nervous

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_54

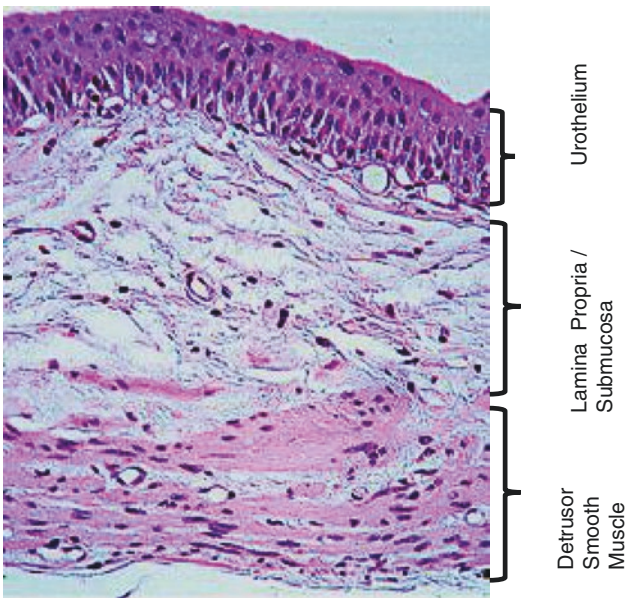

Fig. 54.1 Bladder wall. Image of bladder wall showing the urothelium (outer layer), the lamina propria/submucosa and underlying detrusor smooth muscle

system (CNS) in the control of micturition. One of the pathways defined involves the bladder mucosa, but attention has been given mainly to the urothelium. However, the urothelium may be regarded as one part of a signaling system involving also the lamina propria (LP) [6]. The LP lies between the basement membrane of the mucosa and the muscularispropria (detrusor muscle) and is composed of an extracellular matrix containing several types of cells, including fibroblasts, adipocytes, interstitial cells and sensory nerve endings. In addition, LP contains a rich vascular network, lymphatic channels elastic fibers and smooth muscle fascicles (muscularis mucosae) [7–9]. Notably, the thickness of the LP varies within the bladder. The morphological characteristics of the LP, muscularis mucosae and the detrusor muscle are important for pathological tumor staging of bladder cancer. However, LP is not only a landmark, but also a functionally active structure essential for, e.g., afferent signaling.

54.2.4 Afferent Nerves

Different types of nerves have been described in the LP. In the lower part of the bladder body and bladder neck, there was a gradual increase in the number of nerves and Gosling and Dixon proposed that these nerves may have a sensory function [7]. Throughout the bladder neck itself, the nerves form an extensive plexus adjacent to the urothelial lining. Given the location in close proximity to the urothelium, it is not surprising that changes in urothelial structure and function can occur with either pelvic nerve stimulation or neural activation following spinal cord injury [10].

54.3 Barrier Function

The urothelium plays a critical role as a permeability barrier to urine, and an intact barrier is a prerequisite for normal afferent signaling from the bladder. Several features of the superficial or umbrella cell layer aid the bladder in maintaining normal barrier function as the bladder fills and empties. These include a number of tight-junction proteins in addition to specialized lipids and uroplakin proteins in the umbrella cell apical membrane. The uroplakins have important functions including maintaining the urothelial barrier in part by preventing proteins as well as ionic and nonionic substances from gaining access [10]. In addition, a layer of polysaccharide GAG or mucin covers the superficial urothelium and may have a number of roles including a defense mechanism against microorganisms, carcinogens and toxic substances in the urine. The lipid composition of the apical membrane is unusual and is rich in cholesterol, phosphatidylcholine, phosphatidylethanolamine and cerebroside [12]. Recent studies suggest that liposomes, consisting of an aqueous core enclosed in one or more phospholipid bilayers, may help to restore urothelial-barrier functions. Liposomes have typically been used to transport drug molecules in a variety of cells. Urothelial cells appear to take up liposomes via an endocytotic process, providing evidence for a possible mechanism by which liposomes act as a drug delivery system [13]. In addition, empty liposomes have shown promise to repair and enhance the barrier function of a dysfunctional urothelium [14, 15] (Fig. 54.2).

Epithelial integrity is maintained through a complex process of migration and proliferation (to restore cell numbers) and differentiation (to restore function) [16]. Basal epithelial cells, which have been suggested to have stem-cell-like properties, typically exhibit very slow proliferative rates [12]. However, upon using agents that damage the umbrella cell layer (protamine sulfate, cyclophosphamide), it has been shown that the urothelium rapidly undergoes both functional and structural changes to restore the barrier in response to injury [17]. In the early stages of regeneration following disruption of the barrier, superficial cells may appear smaller in size and often covered with microvilli. In some pathologies, a deficiency or defect in maturation or terminal differentiation of superficial umbrella cells have been reported, although the factors that may be involved are not yet known [18]. The processes underlying urothelial repair are complex, involving several structural elements, signaling pathways, trophic factors, and the cellular environment. However, the interaction between these biochemical signals and mechanical forces in the bladder during the course of urothelial repair are not well understood.

Although the urothelium maintains a tight barrier to ion and solute flux, a number of local factors or stressors, such as tissue pH, mechanical or chemical trauma, hormonal

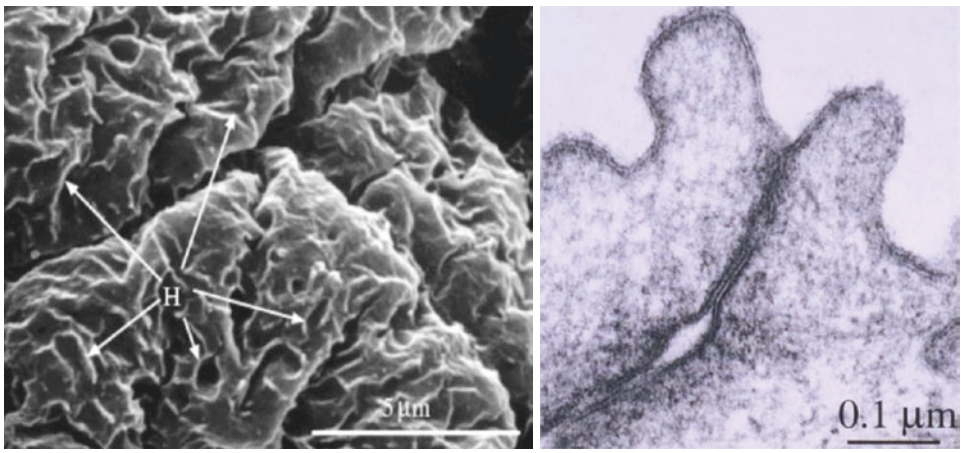

Fig. 54.2 Ultrastructural features of umbrella cell apical membrane. Left: Scanning electron micrograph (high magnification) of apical surface of rabbit umbrella cell layer (hinges "H" marked with arrows). Right, high power view of tight junctions [10, 11]

changes, or bacterial infection can modulate its barrier function [19]. Stress mediated activation of the hypothalamic-pituitary-adrenal axis and autonomic nervous systems can result in increased production of various stress mediators, which can lead to a disruption of the epithelial barrier and even increased prevalence of infection. Conditions such as IC/BPS or spinal cord injury have been associated with changes in the urothelial barrier. Disruption of urothelial barrier integrity has been linked to the expression of substances such as antiproliferative factors (APF), which also slows urothelial cell growth. AFP, a frizzled 8 protein detected in the urine of patients with IC/BPS, is secreted by bladder urothelial cells obtained from these patients [20]. Treatment of urothelial cells from normal patients with purified APF decreased the expression of adhesion and tight junction proteins.

Both physiological and psychological stress can result in a failure of urothelial and suburothelial 'defensive' systems and thereby promote changes in both urothelial barrier and signaling function. For example, alterations in proteins including proteoglycans and bacterial defense molecules may lead to distinctive changes in urothelial structure and play a role in bacterial adherence [21]. Even acute contact (within hours) of the mucosal surface by bacteria may result in altered urothelial bacterial function. Although the urothelium maintains a tight barrier, a number of factors (mechanical or chemical trauma, infection) can modulate the barrier function. When the barrier is compromised, the urothelium is unable to maintain the integrity of the bladder-urine interface. The result can be changes in the function of underlying cells within the bladder wall and sensory symptoms of urgency, frequency, and pain during bladder filling and voiding. Thus a complex chemical information transfer exists between the urothelium and cells within the bladder wall and disruption in this 'sensory web' may be involved in bladder dysfunction.

54.4 Sensory Web

It is likely that a cascade of urothelial inhibitory and stimulatory transmitter/mediators are involved in the transduction mechanisms underlying the activation of afferent fibers during bladder filling [6]. The mucosal activation pathway ('sensory web') includes the urothelium, the afferent (and efferent) nerves as well as the muscularis mucosae. It is clear that communication between these different structures ensures normal function of the organ and may explain how the effect of various neurotransmitters/mediators when given intravesically can modify bladder function by changing the neurotransmission, the spontaneous activity of the detrusor smooth muscle and thereby bladder function (Fig. 54.3).

There is substantial evidence that the urothelial cells are able to respond to a number of stimuli (physical as well as chemical). In turn, the urothelium can signal (via substances they release, often termed volume regulation) to cells in the bladder wall. In this manner, the urothelium is likely to play an important role in the complex transfer of information to and from the nervous system. The urothelium is able to respond to a wide variety of mechanical stresses during bladder filling and emptying by activating a number of possible transducer proteins. Possibilities of mechanical signals include bladder pressure, tension in the urothelium or bladder wall, torsion, geometrical tension and movement of visceral organs. Recent studies have demonstrated that urothelial cells release transmitters (such as ATP) during changes in hydrostatic pressure (in ranges that normally trigger micturition) [22, 23]. The urothelium can also respond to changes in urine tonicity. Alterations in the composition of urine are a type of stress; the urine contents can vary in both their rate of delivery as well as the particular constituents.

Additional lines of evidence suggest that urothelial cells participate in the detection of both physical and chemical

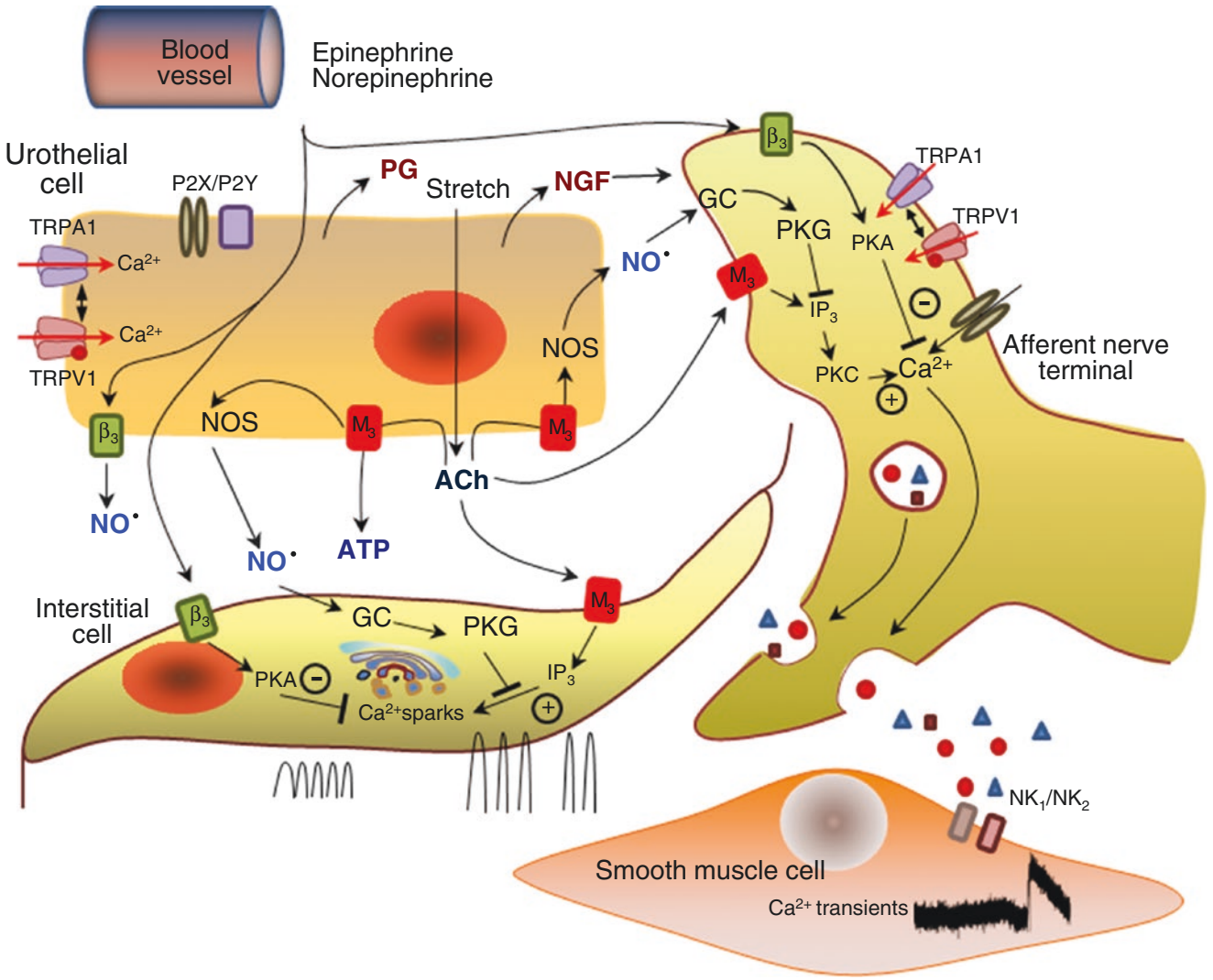

Fig. 54.3 Hypothetical model depicting possible interactions between bladder nerves, urothelial cells, smooth muscle, interstitial cells and blood vessels. Urothelial cells can also be targets for transmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e. auto regulation) or paracrine (release from nearby nerves or other cells) mechanisms

stimuli [2, 19]. As mentioned, bladder nerves (afferent and efferent) are localized in close proximity to, and some within, the urothelium. In addition, urothelial cells express numerous receptors/ion channels similar to what is found in both nociceptors and mechanoreceptors elsewhere in the body, and these cells secrete a number of transmitters or mediators capable of modulating, activating, or inhibiting sensory neurons. Examples of neuronal 'sensor molecules' (receptors/ion channels) that have been identified in urothelium include receptors for purines, adenosine, norepinephrine, protease-activated receptors, bradykinin, neurotrophins, estrogens and various TRP channels. The expression of these various receptors enables the urothelium to respond to a number of 'sensory inputs' from a variety of causes. These inputs include increased stretch during bladder filling, soluble factors (many found in the urine), or chemical mediators/peptides/transmitters released from nerves, inflammatory cells and even blood vessels. Thus various stimuli can lead to secretion of chemical substances capable of modulating the activity of underlying smooth muscle as well as nearby sensory neurons. For example, urothelial-specific overexpression of nerve growth factor (NGF) results in increased bladder nerve 'sprouting' and increased voiding frequency [24]. It has been shown that urothelial-derived nitric oxide (NO) can be released in response to mechanical as well as chemical stimulation and may either facilitate or inhibit the activity of bladder afferent nerves conveying bladder sensation [25, 26]. In this regard, activation of urothelial receptors and release of inhibitory mediators may explain, in part, the mechanism of action for therapies (e.g., beta-3 AR agonists) in treatment of bladder disorders such as the overactive bladder (OAB) [27].

In addition, there is evidence that epithelial cells in different organ systems may express similar receptor subtypes. Accordingly, epithelial cells could use multiple signaling

pathways, whose intracellular mechanisms differ according to location and environmental stimuli. This would permit a greater flexibility for the cell to regulate function and respond to complex changes in their surrounding microenvironment. Whether urothelial-sensor molecules all feed into a diverse array of signaling pathways or share similarities with systems such as olfaction, whereby hundreds of receptors share identical transduction cascades, is yet to be uncovered.

54.5 Changes in Bladder Disorders: Bladder Pain Syndrome

A hallmark of chronic visceral pain syndromes, including IC/BPS, is pain excluding other demonstrable visceral pathology. At present, there is no known etiology nor treatments that can effectively diminish or abolish the symptoms. The diagnosis of IC/BPS is based on symptom criteria which include suprapubic pain associated with bladder filling often accompanied by a strong desire to void and increased frequency of urination. In addition, overlapping or chronic conditions (such as OAB) often share a number of similar features (such as urgency and suprapubic pressure) [28].

IC/BPS has often been described as a disease of the urothelium [29]. Ultrastructurally, an altered vascular supply is observed in its ulcerative form with locations of moderate-to-severe redness, interspersed among a whitish discoloration. There is also evidence that the urothelium in IC/BPS is associated with altered synthesis of a number of proteins including those involved in cellular differentiation, barrier function and bacterial defense mechanisms. In this regard, studies have shown in patients diagnosed with the ulcerative form of IC, that laser removal of damaged urothelium is associated with reduction of symptoms of bladder or pelvic pain [30]. This treatment stimulates a rapid urothelial turnover, and patients undergoing this treatment report a prolonged period without pain after therapy. In terms of barrier 'repair' instillation of liposomes composed of phospholipids has been shown to support repair of the urothelial barrier in animals following bladder irritation [31]. Although the mechanism is not well defined, by forming a protective coating on the urothelium, liposomes may act as a mucosal protective agent and thereby decrease irritation of underlying afferent nerves. In this regard, use of intravesical liposomes in treating IC/BPS patients [15] has shown promise to repair and enhance the barrier function of a dysfunctional urothelium, although further trials are needed to fully assess this type of treatment (Fig. 54.4).

As mentioned previously, the urothelium is likely to play an important role by actively communicating with bladder nerves, smooth muscle cells, or even cells belonging to the immune and inflammatory systems. Altered expression or sensitivity of molecular targets such as TRPV1, acid-sensing channels and others have been reported in IC/BPS patients as well as in animal models for the syndrome. In addition, augmented release of transmitters, most notably ATP, from the urothelium can lead to painful sensations by excitation of purinergic receptors on sensory fibers both peripherally and centrally. Thus, inhibition of purinergic P2X3 receptors has been shown to be effective in suppress-

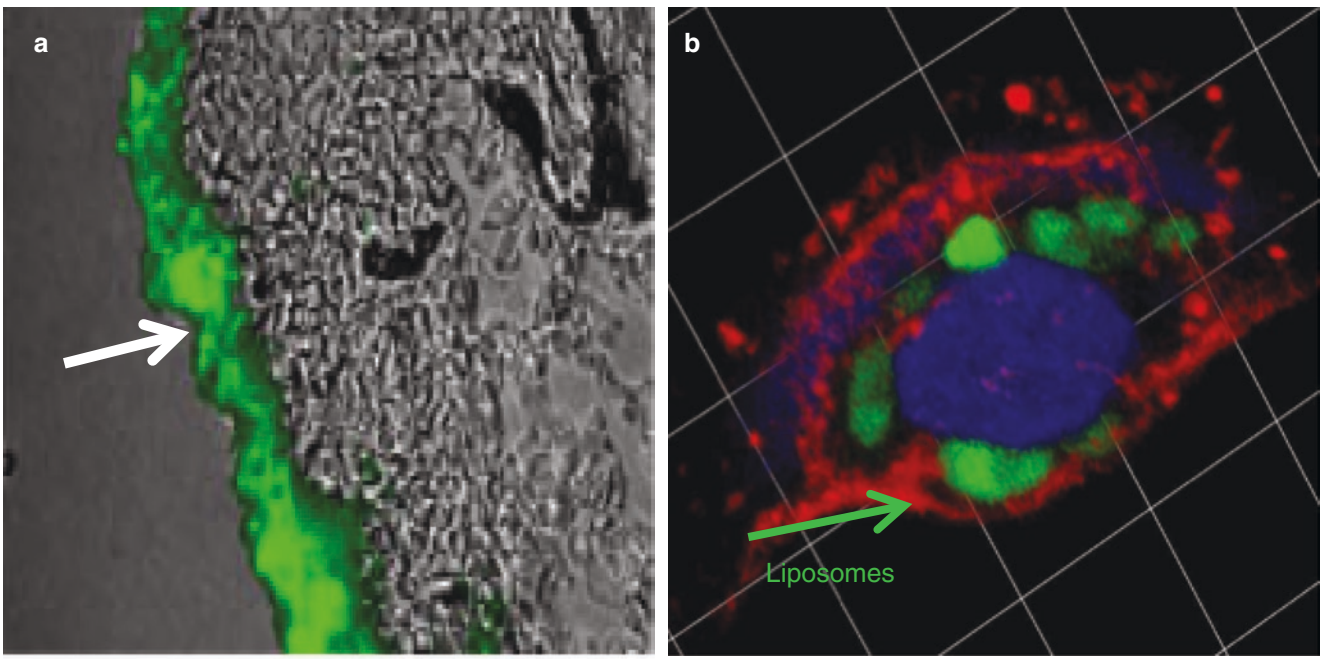

Fig. 54.4 Fluorescent images following application of liposomes. (**a**) Liposomes instilled in a rat bladder forming a coating (green) on urothelial surface and in (**b**), liposomes (in green) attached to primary cultured urothelial cell membrane [13]

ing afferent excitation in various animal models and may be effective in clinical conditions associated with pain such as IC/BPS [23] (Fig. 54.5).

Onabotulinum toxin A (BoNT-A) has been used in the treatment of lower urinary tract disorders including IC/BPS and appears to have a positive therapeutic effect. By inhibiting SNARE-dependent exocytotic processes, BoNT-A can prevent the release of transmitters (such as ATP) as well as normalizing the expression of various receptors, channels and trophic factors [32]. Preliminary studies using immunoblotting indicate expression of the SNARE proteins SNAP23 and SNAP25, as well as the high-affinity binding site SV2, in both rodent and human mucosa [33]. These and other studies suggest that the urothelium may be a target for this treatment and that urothelial-released mediators may contribute to sensory urgency/pain.

There is a great deal of interest in identifying a 'biomarker' that could be of value in the diagnosis (and not just predictive of symptom progression) for IC/BPS. A range of factors have been studied including APF, insulin-like growth factor as well as urinary chemokines and have been shown to be correlated to IC/BPS. While some reports suggest uri-

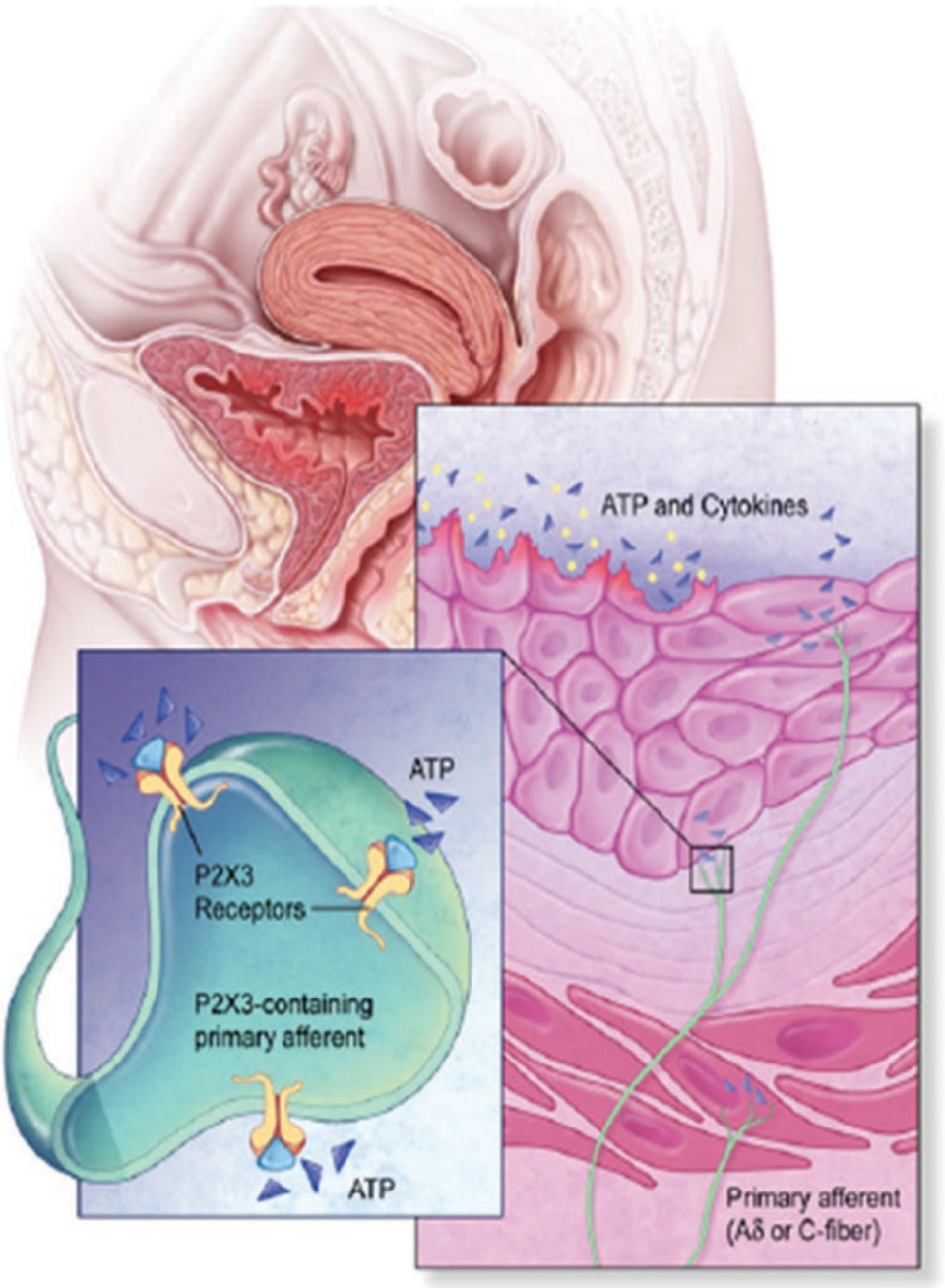

Fig. 54.5 Morphology and wiring of the LUT. ATP is present in large extracellular concentrations, released by various cells including epithelia, fibroblasts and smooth muscles and can activate C-fiber afferents and promote sensitization. Release of ATP is augmented in conditions of stress, injury, inflammation and infection [23]

nary markers may be useful to discriminate IC/BPS and asymptomatic controls, these may not correlate with findings using bladder biopsies. The reason in part may be due to variability in biopsy location, depth of sample (containing different cell types), as well as other technical variations. There is some suggestion that there seems to be more of a proinflammatory state with increased infiltration of mast cells in IC/BPS patients compared with controls. In addition, increased levels of NGF in urine and tissue have been linked with bladder pathologies including patients with idiopathic 'sensory' urgency (urgency without incontinence), overactivity and IC/BPS [34, 35]. A major source of NGF has been shown to come from urothelium, which may contribute to increased neural excitability and emergence of bladder pain in IC/BPS.

54.6 Neurogenic Injury/Inflammation

Neurogenic inflammation of the urinary bladder mucosa is a complex process triggered by the release of inflammatory peptides, Substance P (SP), Calcitonin Gene-Related Peptide (CGRP) and, neurokinin A (NKA) from the afferent neurons in response to various stimuli including antigens, bacterial or viral infection, direct stimulation of sensory nerves or other irritants. This process is characterized by an intricate interplay between vascular, immune and nervous systems and results in alterations in all bladder wall components (urothelium, smooth muscle, nerves, blood vessels, and other cells types), leading to dysfunctional voiding and pain. Clinically, neurogenic inflammation of the urinary bladder mucosa may be present in a percentage of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) [36, 37] prostatitis, urethritis, radiation cystitis [38] and spinal cord injury [39]. Patients experience pain in the pelvic area and voiding dysfunction typically characterized by increased frequency, urgency and nocturia. Although difficult to diagnose, the involvement of neurogenic inflammation in these patients is supported by (a) tissue biopsies which present a number of characteristic features of neurogenic inflammation (such as increased mast cells, angiogenesis) and (b) functional studies using intravesical instillation of capsaicin/resiniferatoxin (RTX), and/or bladder hydrodistention, that presumably deplete C-fibers from neuropeptides, resulting in improvements in voiding function and pain relief.

Animal models and human studies provided substantial evidence for the involvement of C-fibers, particularly those expressing TRPV1 receptors, in neurogenic inflammation. Initial experiments using capsaicin have established that both SP and CGRP can be released from the bladder afferents [40]. Further, manipulations including stimulation of dorsal spinal roots [41], intravesical instillation of mustard oil [42], E. coli LPS [43], intravenous injection of SP [43] and virus-induced cystitis [44], have been shown to evoke plasma extravasation in rodent bladder. In many of these manipulations, plasma extravasation was diminished and/or prevented by desensitizing C-fibers with systemic capsaicin treatment, performed neonatally or several days before the terminal experiments, or by denervation of the bladder. Mast cell degranulation, which is another prominent feature described in bladder tissue was also reduced by desensitization of C-fibers, as shown in rodent models of immobilization stress [45] or virus induced cystitis [44, 46]. Clinical studies in patients with IC/BPS and neurogenic detrusor overactivity (NDO) due to spinal cord lesions demonstrated that capsaicin/resiniferatoxin (RTX) instillation into the bladder results in improved bladder function: reduction in the number of micturition episodes per 24 h, number of episodes of micturition associated with urgency per 24 h, number of episodes of incontinence and increased bladder capacity. Additionally, in patients with IC/BPS, hydrodistention alone which presumably depletes afferent nerves from neuropeptides, or in combination with intravesical RTX, provides pain relief [47–51].

Vasodilation and increased vascular permeability are prominent features of neurogenic inflammation. Vasodilation is primarily mediated by CGRP acting on receptors on the vascular smooth muscle [52, 53]. For example, in the pig bladder, CGRP does not affect the smooth muscle contractility but potently dilates the blood vessels via a direct action on the vascular smooth muscle (i.e. removal of the endothelium or nitric oxide synthase inhibition does not prevent the effects of CGRP) [54]. In addition, SP also causes vasodilation [55] by acting on NK1 receptors on the vascular smooth muscle. Vascular permeability is primarily mediated by SP and NKA acting on NK1 receptors, which are abundant in the endothelial cells and the smooth muscle of the blood vessels. Indeed, NK1R antagonists were able to reduce/block SP-induced plasma extravasation, commonly measured in animal models by the Evans blue method [55, 56]. Morphological analysis of the tissue from patients and animal models shows areas of leukocyte infiltration, edema, mast cells [57] and bladder wall glomerulations ('pinpoint bleeding') suggestive of fragile blood vessels (review [58]). A recent study using intravital microscopy methods imaged *in vivo* interactions between leukocytes and endothelial cell in the microcirculatory system following capsaicin application to the serosa surface of the bladder [59]. The experiments revealed a rapid (within 15 min after application) and long lasting (over 45 min) increase in the dynamic of leukocyte rolling and adhesion to endothelial cells accompanied by increased immunoreactivity for the adhesion proteins E-selectin and ICAM-1. These interactions, which are likely involved in leukocyte infiltration in the tissue, are

dependent on the activation of C-fibers (as they were prevented by capsazepine or neonatal systemic capsaicin treatment) and involve CRGP and NK1 receptors. Leukocyte rolling was prevented by a CGRP receptor antagonist ($CGRP_{8-34}$) but not by an NK1 receptor antagonist (RP67580), while the adhesion was prevented by blocking either CGRP or NK1 receptors. Taken together, these findings suggest that the dynamics and extent of neurogenic inflammation processes depend not only on the density of the TRPV1 positive fibers, but also on other factors such as the density of CGRP receptors and the expression of adhesion molecules in the tissue.

54.7 Urethral Sensation

Similar to the bladder uro-epithelium, the urethral epithelium is likely to be part of a signaling system involving projections of neuroendocrine cells, interstitial cells and sensory nerve endings [60–62]. There is speculation that these urethral-neuroendocrine cells (sometimes called paraneurons) could also release mediators, such as serotonin, which through activation of adjacent sensory nerves can stimulate urethral reflexes [60]. Such types of cells are not unlike that in other types of epithelia, such as the trachea, where a cell type termed 'brush cells' has been described, which are likely chemo-receptive and make contact with nearby nerve fibers [63].

While the epithelium in the region of the urethra is not likely to participate as a barrier, there is some evidence that these epithelial cells play a role in continence and sensation. The mucosal pathway (often referred to as a sensory web) within the proximal urethra also involves a cascade of epithelial inhibitory and stimulatory transmitters/mediators. Release of these factors are involved in a complex transduction scheme underlying the activation of bladder nerves and playing a prominent role in sensation. It has been suggested that symptoms of pain that arise from the lower urinary tract might originate principally from the bladder neck and proximal urethra. The bladder neck and proximal urethra contain the largest density of bladder nerves, and the epithelial cells that line the surface show 'neuronal-like' properties including expression of proteins sensitive to chemical and physical stimuli. The proximity of afferent nerves to the epithelium suggest that epithelial cells could be targets for transmitters released from bladder nerves and/or that chemicals released by epithelial cells influence afferent nerve excitability. Thus, urethral epithelial-neural interactions (through the release of mediators) could lead to a 'urethral instability' that can influence storage and voiding reflexes, and result in symptoms including urgency and pain [64] (Fig. 54.6).

54.8 Bladder Microbiota

In recent years, a number of studies suggest that the human urinary tract contains a diverse microbiota that likely plays an important role in bladder health and disease [66]. It is becoming clear that the urine contains different populations of bacteria and the composition of the microbiota is correlated to urinary symptoms, especially urgency and urinary incontinence [67–69], and associated with response to treatment [69, 70].

The urothelial cells are the first line of defense against pathogens. Studies using uropathogenic *Escherichia coli* (UPEC) infection of the bladder (chronic and acute) have shown apoptosis of the apical urothelial cell layer and inflammatory responses involving release of multiple mediators from the urothelium (such as interleukins and cytokines) [71], which result in structural damage to the urothelial barrier [72–74]. As a result urothelial cells start mounting multiple defense mechanisms to limit inflammatory responses [75]. For example, these cells can secrete pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6 and IL-8 (usually detected in urine following infection), which play important role in the recruitment of phagocytes into the infected bladder or kidney tissue. Additionally, the urothelium may produce antibacterial agents, such as uromodulin (also known as Tamm-Horsfall urinary glycoprotein) which acts to prevent bacteria from interacting with the epithelial cell surface [76], or beta-defensin which restricts bacterial growth [77]. Urinary tract infections (UTIs) are often accompanied by acute and chronic pain. It is believed that the acute pain is related to the release of mediators from the urothelium that produce inflammation and activation of afferent nerves. In addition, there is evidence for both inflammation dependent and independent pain mediated by endotoxin (a glycolipid on the outer membrane of Gram-negative bacteria) interacting with Toll-like receptors 4 [65] and dependent on TRPA1 activation [78] (Fig. 54.7).

Chronic pain post UTI develops in some patients and it can also be reproduced in animal models. Experiments in which activation of TRPV1 receptors was prevented using the antagonist capsazepine or in TRPV1 knock-out mice prior to bacterial infection (with the E. Coli stain SΦ874), revealed that allodynia and increased VMR reflexes (an indicator of nociception) triggered by bladder distention, were prevented [65]. Together, these studies demonstrate that the microbiota by engaging urothelial cells and afferent TRPV1 nerves plays an important role in pain after bladder infection.

54.9 Animal Modeling of IC/BPS

The etiology of interstitial cystitis/bladder pain syndrome (IC/BPS) remains elusive and may involve multiple causes. To better understand its pathophysiology, many efforts have

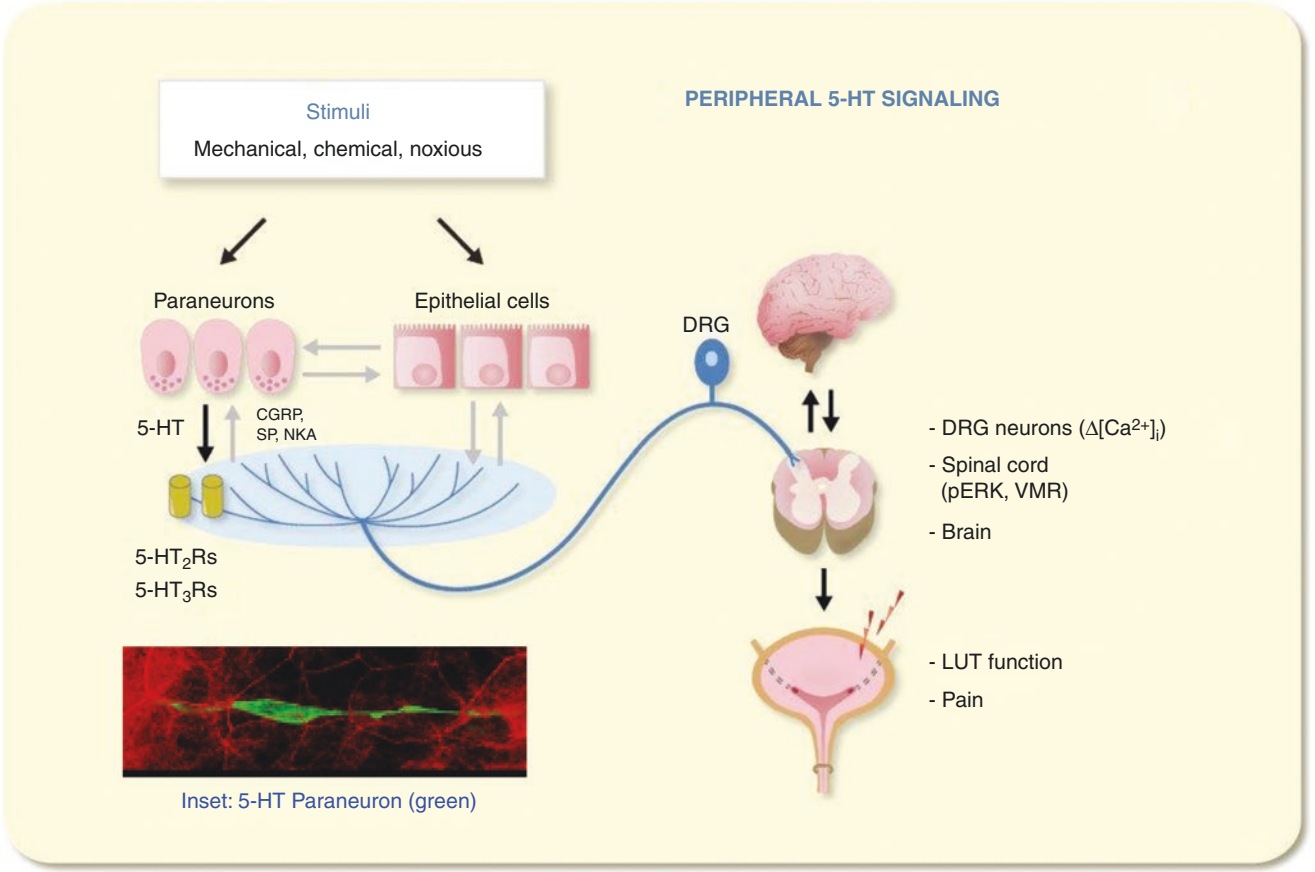

Fig. 54.6 UPEC induces pain. UPEC induces pain separable from other facets of UTI pathogenesis. FimH acts as a tethered toxin that mediates urothelial apoptosis and consequent bladder-barrier dysfunction. LPS plays dual roles through its interactions with TLR4. In addition to triggering inflammation, LPS mediates pelvic-pain responses [65]

been made to create "IC/BPS models". Most existing models of IC/BPS strive to recreate bladder-related features by applying noxious intravesical or systemic stimuli to healthy animals. These models are useful to help understand mechanisms, however limited to demonstrating how the bladder and nervous system respond to noxious stimuli; they are not representative of the complex interactions and pathophysiology of IC/BPS. To study different factors that may be relevant for IC/BPS, at least three different types of animal model are commonly used (1) bladder-centric, (2) complex mechanisms, and (3) psychological and physical stressors/natural disease models. It is obvious that all aspects of the human disease cannot be mimicked by one single model. It might be that several models, each contributing to a piece of the puzzle, are required to recreate a reasonable picture of the pathophysiology and time course of the disease(s) diagnosed as IC/BPS, and thus to identify reasonable targets for treatment.

Bladder centric models (most often rat and mouse) seem to mimic the case where there is a toxic substance in the urine. The bladder-centric models have clear limitations and are focused on what may be appearing in the bladder. Acute CYP administration causes hemorrhagiccystitis which is typical for neither IC or BPS. Repeated administration of low-dose CYP induces "chronic" cystitis, but these models are more appropriately considered to be a "repetitive acute" cystitis models, at least in the rat. Chronic CYP treatment of mice causes urothelialhyperplasia which is not a characteristic of IC/BPS. Agents such as protamine are non-selective and as such, can disrupt the cytoplasmic membrane resulting in cell lysis [80]. This can result in corresponding damage to multiple cell types extending beyond the urothelial layer (unpublished observations) thus should not be considered an appropriate agent for modelling IC/BPS. To date, no available model attempts to mimic particular epidemiologic findings of IC/BPS patients nor accounts for known effect of sustained adult stress on symptom severity. Even if bladder-centric animal models cannot be considered to model the human disease, they are important for elucidating pathological changes and underlying mechanisms in bladder structures associated with chronic inflammation induced in various ways. In contrast, complex mechanisms models are based on the assumption that the causes for the alterations in

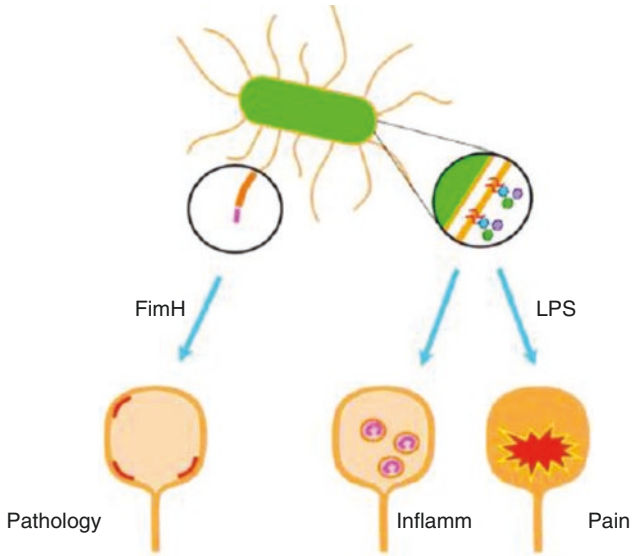

Fig. 54.7 Proposed diagram of peripheral 5-HT signaling. Various urethral stimuli (mechanical, chemical, noxious) reach the paraneurones and epithelial cells. In response, paraneurones release 5-HT that acts on 5-HT2 and 5-HT3 receptors on the afferent nerves (depicted in blue). Information is then transmitted to the dorsal root ganglia (DRG), spinal cord and brain and can influence lower urinary tract (LUT) function and pain/nociception. Additionally, 5-HT can act on epithelial cells that can in turn release transmitters to influence neuronal activity and paraneurons. The afferent nerves can also release peptides, CGRP, SP or NDA to activate paraneurones and/or epithelial cells [79]. Inset: Example of 5-HT positive paraneuron (green) in the mid-urethra illustrating multipolar-like processes, co-stained with phalloidin (red) to delineate the epithelium

the bladder occur elsewhere—for example via activation of the CNS, etc. These can include injection of pseudorabies virus in the tail-leading to bladder changes via activation of CNS circuitry; various 'co-morbid' disorders (instillation of TNBS into the colon; autoimmune models, chronic pelvic pain, vulvodynia) [81–85].

54.10 Impact of Psychological Stress on Bladder Homeostasis

It has been shown that the 'stress response' involves local and systemic increases in signaling via release of corticosteroids as well as catecholamines. This in turn (along with increased expression of a number of pro-nociceptive transmitters) sensitizes pain pathways and can promote a number of visceral pain disorders. Studies have shown that patients which have been exposed to chronic stressors (i.e., post traumatic stress disorder; anxiety) often report a higher incidence of chronic pain. Psychological and physical stressors have been used in preclinical animal models and include various stressor (water avoidance; restraint stress), feline IC model, injection of norepinephrine, manipulation of environmental temperature and also light. While animals cannot self-report whether they can feel 'pain', their behavior in response to a number of noxious or otherwise irritative stimuli can be observed and scored. Recently, studies have shown that other factors including various types of psychological and physical forms of stress can produce either analgesia or hyperalgesia in a number of settings. Even differences in ambient temperature and social factors can alter measures in pain studies. Psychosocial stress can have a significant impact in a number of co-morbid and other diseases including fibromyalgia, skin diseases and even asthma and irritable bowel syndrome (IBS). A wealth of research now has revealed that stress can significantly alter the communication between the (skin, bladder, gut)-brain-axis, and how targeting these types of signaling mechanisms may impact health and disease [86–88]. In addition, IC/BPS patients exhibit increased functional brain activation in the full bladder in brain regions known to participate in sensory perception and pain. In this regard, there is evidence that chronic water avoidance stress (or WAS) in rats predisposed to anxiety can result in a number of clinical and functional features similar to that in humans diagnosed with IC/BPS. Studies have shown that chronic psychological stress induces urinary frequency, sustained bladder hyperalgesia, tactile hindpaw allodynia and suprapublic hyperalgesia. This model also reveals increased engagement of portions of the micturition circuit responsive to urgency [89]. The WAS model has also been shown to exhibit alterations in the GI tract as a model for IBS, which may be a comorbid condition associated with both LUTS and IC/BPS.

While the sequence of events that link psychological stress to functional pain syndromes such as IC/BPS have not been clarified, it is thought that activation of the sympathetic division of the autonomic nervous system may play a key role. The involvement of the sympathetic system has been reported in a number of chronic painful conditions including complex regional pain syndrome and fibromyalgia. For the latter, studies have revealed the sympatho-adrenal stress axis cannot only play a role in the induction but also the maintenance of mechanical hyperalgesia. Adrenergic stimulation has been shown to mediate hypersensitivity of the pelvic viscera: both in terms of long lasting effects on bladder function as well as to colorectal distension. Thus, chronic stress results in enduring changes in the nervous system that alters sympathetic nerve activity which may be one mechanism by which stress enhances the severity and duration of pain symptoms.

54.10.1 Translational Aspect to Animal Models

The etiology of IC/BPS is unknown but may involve multiple causes. It is now generally accepted that IC and BPS may be two different entities—each disorder may require

distinct animal models. However, 20 years ago Elbadawi [90] wrote: "As it now stands, there is no natural or induced animal model that duplicates IC as it occurs in humans." This is true even today. The limited success in translating the vast amount of basic science data using animal models into effective and safe treatments for a variety of pain conditions may be due in large part to the complexities of the human condition itself. Thus, no animal model can be expected to reproduce all the various symptoms experienced by humans. Most available animal models strive to reproduce morphological and functional changes found in the bladders of patients, i.e., are bladder-centric, and may be useful for studies of e.g., inflammatory pathways in IC patients. More complex models are needed for mimicking the symptoms and systemic changes found in BPS patients. All aspects of the human disease cannot be mimicked by one single animal model, and it might be that several models, each contributing to a piece of the puzzle, are required to create a reasonable picture of the pathophysiology and time course of the disease(s) diagnosed as IC or BPS, and thus to identify reasonable targets for treatment.

54.11 Neurogenic Injury/Neuropathic Pain Associated with Spinal Cord Injury

LUT dysfunction and complications are a major concern in the management of spinal cord injured (SCI) patients. In addition, chronic pain (both neuropathic and nociceptive type) is common in these patients. Neuropathic pain, a common complication following SCI, is caused by damage to the nervous system and typically divided into peripheral and central pain [91]. In contrast, nociceptive pain may be due in part to damage to non-neural tissue (i.e., joint, muscle trauma or inflammation). There are a great many changes in receptors and ion channels that occur after SCI and are likely to play a role in the development of bladder and pain symptoms. For example, while C-fiber afferents have a role in the development of hyperactivity in SCI-neurogenic and idiopathic detrusor overactivity (NDO, IDO), there is support for the involvement of the urothelium in these symptoms. For example, antimuscarinics, intravesical vanilloids and also botulinum toxin has been shown to restore urothelial-muscarinic receptor expression to control levels, and these findings also correlated with improvement of patient bladder symptoms. There is also evidence in SCI rodents that NGF (both mRNA and protein levels) are increased in bladder [92]. NGF can mediate a number of processes including cell signaling and can increase expression of a number of ion channels associated with painful sensation such as TRPV1. Changes in TRPV1 expression in patients with neurogenic bladder were found to be normalized in patients responding favorably to intravesical vanilloid therapy [93]. Increases in TRPV1 expression and/or sensitization may play a role in sensory changes including allodynia as reported in models for peripheral nerve injury.

54.12 Therapies and Future Directions

In terms of neuropathic or nociceptive pain after SCI, though a number of therapies have been studied, the best documented effect on SCI-resultant neuropathic pain support the use of tricyclic antidepressants such as amitriptyline as well as antiepileptic drugs such as gabapentin and pregabalin. Other agents used for intractable pain after SCI are the opioids however the side effect profile for these agents may preclude long term use. The NOD-like receptor protein-3 (NLRP3) inflammasome contributes to release of cytokines and other mediators which are likely to contribute to neurologic dysfunction and tissue loss [94]. Thus, suppression of the NLRP3 inflammasome may be a promising new area in terms of attenuating neuroinflammation and the severity of SCI damage. Further, changes in expression of the vanilloid receptor TRPV1 and/or sensitization may play a role in allodynia that have been reported in models for peripheral nerve injury [95]. Alterations in TRPV1 can also result in inhibition of mitochondrial respiration. Mitochondria are considered the powerhouse of the cell that generate 95% of all energy and play a key role in cellular homeostasis [96]. Indeed, the study of bioenergetics and the influence of mitochondrial functions on cell signaling and disease is an emerging and exciting area of research. Mitochondrial dysfunction has been implicated in a number of disorders. These organelles are highly sensitive to changes in their cellular environment and can be easily affected by a number of conditions. For example, there is ample evidence that ischemia leads to cellular damage by overproduction of superoxide by the mitochondrial electron chain. A disruption of mitochondrial functions following a traumatic SCI or chronic pelvic pain can result in altered release of inflammatory mediators including ATP and reactive oxygen species [97]. Though there are currently no available therapies for the treatment of SCI or SCI-associated pain, some promising preliminary studies using antioxidants to enhance mitochondrial function may be a potential strategy to produce neuroprotection and improve function [98].

In terms of bladder pain syndrome, current research approaches including anti-nerve growth factor treatment, anti-tumor necrosis factor-alpha treatment, activation of SHIP1 (AQX-1125) and P2X3 receptor antagonists have all been tested with mixed success. In addition, local treatment approaches such as the antagonism of Toll-like receptors (experimental) and intravesical liposomes (with positive proof-of-concept) may have advantages of low number of systemic adverse effects. However, these treatment approaches cannot be expected to have effects on symptoms generated outside the bladder.

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Neurogenic Bowel Dysfunction

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Gianna Rodriguez and Anne P. Cameron

55.1 Introduction

Severe debilitating lower urinary and bowel dysfunction is unfortunately common in patients with neurological conditions such as spinal cord injury (SCI), multiple sclerosis (MS), spina bifida and transverse myelitis on top of their physical disabilities. Despite the extraordinarily high prevalence of neurogenic bladder (87–95%) [1, 2] and neurogenic bowel (62–95%) [3, 4] in these populations, only the bladder has received the attention of medical providers with neurogenic bowel physiology is less understood and characterized compared to neurogenic bladder [5]. Neurogenic bowel has a significant impact on these patients and is characterized by combination of symptoms including lower gastrointestinal symptoms of constipation, diarrhea and or fecal incontinence. It could also have upper gastrointestinal impairment which can lead to bloating, nausea earlier satiety, reflux symptoms and gaseousness [6–10].

Other less obvious symptoms secondary to neurogenic bowel include autonomic dysreflexia [11], decubitus ulcers and failure to thrive due to poor appetite. Less life threatening complications, but no less bothersome to patients include hemorrhoids [12], fecal impaction, constipation, fecal incontinence, abdominal pains and bloating [3, 7, 13]. Long times spent performing bowel regimens and social isolation from fear of having an accident are also very bothersome to patients who already have great difficulty leaving their homes [10, 14].

Constipation and/or fecal incontinence create considerable psychological, social, and emotional distress. These dysfunctions can significantly impact rehabilitation and return to their homes. Unfortunately, these disorders tend to worsen rather than get better over time [10]. Bowel and bladder complications have been shown to have the most noteworthy impact on more than 30% if people with SCI, 41% indicating that bowel issues are extremely life restricting [15]. However, acute rehabilitation is unable to address all the knowledge and the skills a person with SCI must have to address bowel care despite gaining ability to deal with other problems like mobility and activities of daily living [3, 7].

Inefficient management of the bowels in one third of people with SCI results to progressive decline in bowel function 5 years after injury causing megacolon in 33% [16, 17]. Fecal incontinence increases cost burden in nursing homes especially with the increased risk of skin breakdown [18]. Keeping bowel health optimal with maintaining regular bowel movements is as imperative as social continence. In people with SCI, social continence can be achieved with timed, expected defecations without episodes of incontinence [10]. Continence is crucial not only to decrease other health care risks but to decrease stress and worry from embarrassing situations which adversely affects the ability to be productive and engage in work and vocational activities [10].

Urologists frequently manage neurogenic bladder in patients with neurological conditions and given the coexistence of neurogenic bowel with this condition should be competent at managing basic bowel management, but unfortunately typically are not. Many patients do not have access to rehabilitation specialists and the urologist must be aware of this condition and basic treatment as well as indications for referral. Patients often have dual incontinence and solely addressing one of these disorders will not get a patient out of absorbent products. Like neurogenic bladder, neurogenic bowel can result in significant complications particularly when accompanied by bladder dysfunction or bladder incontinence. Dual incontinence puts this vulnerable population, often with limited mobility and perineal sensation at high risk for pressure ulcers [1]. The social and vocational implications of dual incontinence cannot be overemphasized. Also there is emerging evidence that better treatment of constipation with elimination of fecal incontinence episodes with trans anal irrigation may lower the rate of bladder infection [19]. It has also been shown in patients with SCI, MS and

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_55

spina bifida that worse neurogenic bladder correlates with worse neurogenic bowel, however the mechanism for this association still has not been elucidated [20].

Neurogenic bowel problems occur in brain disorders like stroke, brain injury, Parkinson's disease, in spinal cord disorders like spinal cord injury, spina bifida and in peripheral nerve injuries. Neurologic disease unfortunately has direct effects on gut function in addition to poor mobility, inadequate water intake, intake of opiate analgesics, anticholinergics and other medications [6, 9, 21, 22].

55.2 Pathophysiology of the Neurogenic Gut

Neurologic disease can affect different portions of the gastrointestinal tract exemplified by gastro-esophageal, small intestinal and colon dysmotility and impaired sensation resulting to impaired function [10].

Nausea, vomiting, bloating, early satiety. The constellation of nausea, vomiting, bloating, and/or early satiety is often a sign of motility problems in the gastrointestinal tract secondary to neurologic conditions provided there is no mechanical obstruction. These symptoms arise from spasticity of the gastric or intestinal/colonic musculature caused by neurologic dysfunction involving specifically the inhibitory motor neurons in the ENS at any level of the neural axis from the brain, spinal cord, afferent and efferent nerves [10]. There is a persistent discoordinated contraction of the circular muscle preventing propulsion distally producing functional obstruction when these inhibitory neurons are altered by disease in the autonomic, myenteric or smooth muscle systems [23, 24]. This can present with dysphagia, gastroparesis or chronic intestinal/colonic pseudo-obstruction which can be coupled with anorexia, abdominal pain and diarrhea and constipation [24, 25].

Abdominal Pain and Discomfort. Gut distention and forceful contractions can result in abdominal pain and discomfort in neurogenic bowel. In the gastrointestinal tract, high threshold and silent mechanoreceptors perceive significant distention and powerful contractions when there is ischemia, injury, inflammation, or obstruction. The brain and spinal cord receive signals from mechanical and chemical irritants which excite mechanoreceptors in the ENS from muscle stretch and contractions [24, 26, 27].

Diarrhea. Diarrhea in the setting of neurologic dysfunction is typically due to overflow constipation. However, it can be due to over activation of secretomotor neurons by histamine from inflammatory and immune mediated cells in the mucosa and submucosa and/or vasoactive intestinal peptide and serotonin from mucosal enterochromaffin cells. These chemicals in turn affect presynaptic inhibitory receptors to impede the release of norepinephrine from postganglionic sympathetic fibers that inhibit secretomotor neurons [24, 28].

Defecation Dysfunction. Defecation dysfunction is prevalent in neurologic brain and spinal cord disorders, sacral, hypogastric and pudendal neuropathy presenting as constipation, fecal incontinence or both. Constipation occurs due to irregular evacuation of hard stools caused by reduced secretion of water and electrolytes into the intestinal lumen from inhibition of secretomotor neurons in the ENS [24, 29]. Hyperpolarization of the secretomotor neurons ensues when firing is inhibited by norepinephrine release by sympathetic stimulation. There is diminished secretion of water and electrolytes with the emission of excitatory neurotransmitters. Prolonged colonic motility, and loss of perineal and rectoanal sensation can lead to outlet obstruction [24]. Impaired rectoanal and perineal sensation, abnormal and discoordinated pelvic floor muscles and external anal sphincter further contributes to the issues with constipation which can alternate with true fecal incontinence [10], defined by lack of awareness and unexpected passage of stool. Internal sphincter and pelvic floor weakness resulting from involvement of the sacral cord, cauda equine, s2–4 nerves, pudendal and pelvic nerves and amplified parasympathetic influence can promote more issues with incontinence and difficulty with defecation [5, 30].

55.2.1 The Upper Motor Neuron Bowel

Lesions in the central nervous system above the sacral segments present with upper motor neuron (UMN) bowel model of dysfunction. There is diminished urge to defecate due to impaired spinal cortical sensory pathways although people with SCI may have some perception of rectal or colonic distention [10]. In 43%, there is abdominal discomfort that is relieved by bowel evacuation [17, 31]. It has been demonstrated in SCI that there is a decrease in colonic compliance with induced rapid pressure rise and hyperreflexic response with continuous infusion of saline [32, 33]. However, other studies have displayed normal colonic compliance in people with SCI with UMN bowel [31, 34]. In addition, resting sphincter tone has been exhibited to be increased with passive filling of the rectum associated with increased external sphincter pressure [35]. In this type of rectal sphincter dyssynergia, it was shown that intermittent or slow filling of the rectum appears to be associated with normal bolus accommodation and pressure relaxation, although this was incorrectly regarded with decreased colonic compliance [31].

SCI affects colonic motility and stool propulsion demonstrated by Krogh, et al. with colonic transit testing using

swallowed markers and serial radiographs [36]. Motility was found to be delayed in the ascending, transverse, and descending colon, and rectosigmoid in subjects with chronic supraconal SCI and total gastrointestinal transit time averaged 3.93 days (1.76 controls). To evaluate influence of sympathetic innervation, mean total gastrointestinal transit times were compared for patients with lesions above T9:2.92 (±2.41) and from T10 down to L2:2.84 (±1.93). There were no significant differences found even with comparisons of segmental times. In addition, SCI subjects with complete UMN lesions were studied in the acute (5–21 days) and chronic (6–14 months) phases revealing total gastrointestinal transit time was longer during the acute rather than the chronic phase. It was also found that there slower transit throughout the colon with less severe rectosigmoid dysfunction [36].

Normally, the internal sphincter relaxes when rectal distention is present. The external sphincter may relax with evacuation of stool when there is significant rectal distention. In people with UMN bowel, rectal sphincter dyssynergia may occur as a response to increased abdominal pressures since vesicorectal reflex which increases external sphincter pressure remains intact, contributing to difficulty with defecation [37, 38]. People with UMN bowel typically have normal or increased anal sphincter tone, intact anocutaneous (anal wink) and bulbocavernosus reflexes [6].

55.2.2 The Lower Motor Neuron Bowel

Lesions affecting the sacral segments of the spinal cord, cauda equina, peripheral nervous system such as polyneuropathy, or the pudendal nerves present with lower motor neuron (LMN) bowel model of dysfunction [10]. There is overall loss of or decrease in reflexes including the anocutaneous, bulbocavernosus reflexes. The LMN bowel affects the external sphincter under somatic control and the internal sphincter under autonomic control. Coupled with pelvic floor muscle weakness, this is characterized by poor anal tone from sphincter weakness, shortened anal canal (compared to the normal 2.5–4.5 cm length) and non-palpable puborectalis muscle ridge. Overstretching of the sphincters and pelvic floor muscles impairs the ability to hold stool in the rectal vault causing fecal incontinence [37].

Sympathetic and parasympathetic innervation may also be impaired in the LMN bowel. Slow motility is a manifestation of a disrupted parasympathetic system. Colonic transit tests reveal prolonged transit through the rectosigmoid region with diminished activity from the conus which results to significant constipation [36]. This makes the LMN bowel particularly challenging in addition to the baseline issues with fecal incontinence. Fecal loading of hard stool, a consequence of colonic inertia can overstretch the weakened anal mechanism contributing to paradoxical liquid incontinence around a low impaction is and is frequently accompanied by rectal prolapse [37, 39, 40].

55.3 Diagnostic Workup

55.3.1 History

The GI history should be a complete review of symptoms and general neuromuscular and GI function. The inquiry must include problems with abdominal discomfort/pain, bloating, early satiety, nausea, constipation and fecal incontinence. A thorough assessment of diet, fluid intake, activity, medications and current bowel regimen is required. The patient's medications must be evaluated for its effects on slowing motility, specifically opiates, anticholinergics, antispasmodics, etc. Existing bowel care should be outlined including bowel medications and techniques to facilitate bowel movements, timing, amount and consistency of stool outputs. Premorbid bowel history should be explored including prior GI disease or dysfunction, defecation patterns. Questions about urgency, frequency, voluntary control of defecation, episodes of fecal incontinence, required assistance should be asked [10].

There are a few disease specific validated measures of neurogenic bowel function. Tulsky and Hubert developed and validated the SCI-QOL Bladder Management Difficulties and Bowel Management Difficulties item banks and short forms and the SCI-QOL Bladder Complications scale [41]. These are available as computer adaptive tests with 15 items on bladder, 26 on the bowel and five related to bladder infections. There also exit the more widely used Neurogenic bowel dysfunction score [42]. that includes questions on fecal incontinence, constipation, obstructed defecation and quality of life as well as how these are managed. The score can be calculated from points given to each question which are differently weighted and patients can be classified as minor or very minor (0–9), moderate (10–13) or severe (14–47).

55.3.2 Physical Examination

A complete physical examination consists of not only evaluation of the GI system but also of general condition, function, and musculoskeletal and nervous systems. Ideally, this should be done on an annual basis for patients with neurologic disorders since their condition may have changed [10]. The patient may display signs of poor nutrition and

dehydration. The abdomen must be evaluated for distention, bowel sounds, palpation for pain, hard stool and other lesions. A tympanitic abdomen, with distention, hypoactive bowel sounds may indicate gastroparesis, intestinal and/or colonic pseudo-obstruction and in SCI, may be associated with autonomic dysreflexia. A rectal and pelvic and floor examination must be completed. Inspection of the anal area might reveal a puckered sphincter indicating spasticity or a gaping orifice indicating loss of tone. Sensation to pinprick and light touch around the anus and to deep pressure on digital rectal examination must be assessed. Presence or absence of the anocutaneous (mediated by the inferior hemorrhoidal branch of the pudendal nerve, S2–S5) or the bulbocavernosus reflex must be completed. The pelvic floor, perineum and anus should be observed for perineal descent and sphincter relaxation with simulated defecation or the Valsalva maneuver both grossly and with digital examination. Internal and external anal sphincter tone, voluntary squeeze strength and pelvic floor integrity should also be evaluated grossly and with digital examination together with the ability to voluntarily contract, relax and coordinate these muscles. The puborectalis muscle sling can be palpated on the posterior wall 1.5–2.5 cm from the anal verge and when intact, the finger on examination is pushed forward when defecation is resisted by the patient. Puborectalis atrophy and dysfunction is noted if there is no palpable ridge or forward push [10].

55.3.3 Diagnostic Testing

History and physical examination should guide the need for diagnostic tests.

- Testing for intrinsic GI disease and non-neurologic conditions (celiac, Crohn's, inflammatory bowel disease, etc.) is best served by the GI specialist.
- Abdominal x-ray may be useful in determining fecal loading and/or impaction, obstruction, megacolon or perforation. More detailed radiographic testing for other issues may be done with CT scan.
- Testing for GI transit with gastric emptying study, small intestinal bowel through and colonic transit testing or the wireless manometry capsule may reveal gastroparesis, delay in small intestinal or colonic motility [10].
- Anal rectal manometry with balloon expulsion test is helpful in evaluating pelvic floor and internal/external anal sphincter function, strength/relaxation, and coordination, rectal sensation and pressures, and simulated defecation.
- Defecography assesses defecation dynamically under fluoroscopy and helpful in identifying structural impairments in the pelvis like rectal prolapse, rectoceles and cystoceles as a cause of defecation issues.
- Colonoscopy, sigmoidoscopy and anoscopy are used to assess for structural and anatomic lesions e.g. colon or rectal cancer, hemorrhoids, etc. [10].

55.4 Therapeutic Options

55.4.1 Treatment of Constipation and Fecal Incontinence

Management of constipation and fecal incontinence due to defecation dysfunction and loss of voluntary control of bowel movements entails a Bowel Program and/or Bowel Care—a comprehensive, individualized plan with the main intention of preventing complications. It involves use of bowel medications, techniques, devices and education, access to facilities, scheduling, and caregiver requirements. This likewise includes diet, fluids, activity, exercises, and reducing constipating medications [6, 10, 43].

It is vital that the goals of the bowel program and/or bowel care be delineated, keeping in mind that people respond differently to medications and techniques, have different habits, lifestyles and access to resources [10]. There are a variety of normal bowel patterns and stool consistencies. Ninety-five per cent may range from bowel movements three times per day to three times per week with stool consistencies from watery, pasty, semisolid, soft formed, hard [43, 44] To optimize evacuation of stool and preclude incontinence, goals of the bowel program and/or bowel care [10]. consists of: 1-routine stool elimination daily or at least three times per week; 2-bowel evacuation at a regular hour of the day; and thorough removal of stool from the rectum in every bowel care session, 3- and limiting stool occurrences to once a day, 4. keep the consistency of stools soft, formed (Bristol Stool Type 4-5) [45] and preventing hard stools (Bristol Stool Type 1-3) [45], 5. achieving bowel care ideally within 30 min, at most within an hour [10, 43, 44].

The individual's prior bowel habits can dictate the selection of frequency and scheduling of bowel program and/or bowel care. Designing this should start at the onset of the acute neurologic injury/condition. More consistent daily or every other day stool elimination may decrease major issues with constipation and stool impaction. Scheduling and timing routine bowel program and/or bowel care gives the individual control over bowel movements, allowing planning and predictability. Complete evacuation of the rectum during bowel program and/or bowel care minimizes risk of unplanned stool outputs and frequent stooling [10]. This can be achieved with use of bowel osmotic and stimulant medications, supplemented with initiating defecation with use of rectal medications and/or mechanical techniques (digital stimulation) to permit consistency, regularity and habituation. The individual must be as independent as possible and

take responsibility for their own bowel program and/or bowel care [10, 43, 44, 46].

55.4.2 Nutrition

In most neurologic diseases, colonic transit times are delayed thereby making food and fluid selections essential since these affect the consistency of stools [10]. The goal is to produce soft, formed, bulky stools to ease passage through the colon. Stools harden with delayed motility through the colon due to increased fluid resorption with ensuing constipation. Hard stools lack elasticity and are not moved appropriately through the haustra, making it more difficult to eliminate [10]. High fiber foods maintain more fluid in the stools, improve bulk and elasticity and decrease colonic pressures [40]. Total dietary fiber consumption recommended from food is 25–30 g [46, 47]. Sufficient fluid intake of 2.5–3.0 L (preferably water, non-caffeinated) [48], when taking a high fiber diet is crucial so that this does not cause constipation. High caffeinated drinks like coffee, tea, energy drinks can lead to dehydration from diuresis [10]. Natural fiber from vegetables, fruits, and grains is preferred although supplemental fiber such as psyllium (Metamucil™, Fiberall™), calcium polycarbophil (Fibercon™), and methylcellulose (Citrucel™) may be used as a substitute. The effects of fiber should be assessed in each person and intake should be titrated appropriately [46, 47]. High pressures in the colon from solid stool results to 90% of hemorrhoids and diverticula formation in the general population and 70% of SCI patient [6]. It also promotes persistent straining and can cause peripheral neuropathy in the anal sphincter [6].

For the most appropriate approach to management, the UMN bowel must be defined from the LMN bowel. Brain and spinal cord disorders above T12 present with UMN bowel and spinal cord disorders below T12 present with LMN bowel [10].

55.4.3 Treatment of Upper Motor Neuron Bowel

In the UMN bowel, defecation can be initiated by stimulating the defecatory reflex with digital stimulation, rectal stimulant medication, enemas, or electrical stimulation [10]. These techniques cause reflex relaxation of the IAS and the EAS and elicits anorectal colonic reflexes and enhances left colon motility and assists with evacuation of stool [49, 50].

The digital rectal stimulation method is executed by introducing a gloved, lubricated finger into the rectum and performing gentle circular strokes for 20 s every 5–10 min until the rectum is fully cleared of stool [10].

Rectal medications are used to initiate and maintain reflex defecation. Individuals are instructed to introduce the medication into the rectum 30 min prior to the intended bowel program/care, followed by digital rectal stimulation [10]. The available suppositories are glycerine, vegetable oil based bisacodyl (Dulcolax™), and polyethylene glycol bisect bisacodyl (Magic Bullet™). Other possibilities include mini-enemas, small volume phospho soda enema, bisacodyl enema, and Enemeez™).

Oral bowel medications may be necessary to optimize stool elimination for successful bowel care [10]. Options include stimulants like senna (Senokot™), bisacodyl (Dulcolax™), osmotic agents such as polyethelene glycol (Miralax™), lactulose (Cephulac™), magnesium derivatives (Milk of Magnesia, magnesium citrate), and/or stool softeners such as docusate (Colace™). A combination of stimulant and osmotic medications may be required. Establishing the most suitable regimen will entail trial and error of assorted medications, type dose, duration, frequency and efficacy. It will also require adjustments and modifications of medications as needed based on the goals of the bowel program/care. The individual must be aware that their condition is not static and that they will need regular GI assessment and that their regimen may need to change [10]. There is a high incidence of late GI problems reported in an initially successfully managed SCI population [43].

55.4.4 New Medications to Treat Constipation

There are newer medications available that can be utilized to maintain or improve the bowel program/care [10].

Lubiprostone enhances intestinal and colonic transit by increasing intestinal fluid secretion by activating type 2 chloride channels and assists with passage of stool. It acts on prostaglandin E receptors which aid gastric and colonic muscle contraction and motility [51, 52].

Linaclotide is an agonist of guanylate cyclase-C (GC-C) receptor located on the luminal surface of intestinal epithelial cell. It improves cGMP cyclic guanosine monophosphate (cGMP) which enhances a signal transduction cascade activating the cystic fibrosis transmembrane conductance regulator which results in secretion of fluid into the lumen and promotes intestinal transit [51, 52].

Prucalopride (not available in US) is a selective 5-hydroxytryptamine receptor agonist which stimulates colonic transit and improves constipation by causing high amplitude propagated contractions hence enhancing segmental contractions [53].

Methylnaltrexone and Alvimopan are peripherally acting μ-opioid receptor antagonists which selectively block μ-receptors outside of the CNS and improves constipation related to use of high dose opioids. These have been shown

to improve constipation without reversing analgesia and or prompting opioid withdrawal [54].

55.4.5 Treatment of Lower Motor Neuron Bowel

The LMN bowel is characterized by pelvic floor and sphincter weakness and decreased reflexes. The most efficient method to evacuate stool is by manual disimpaction or flushing enemas (with water plus milk of molasses, soap suds or mineral oil) once or twice a day [10]. Due to increased risk of fecal incontinence, stools must be kept soft, formed and bulky. Oral stimulant and/or osmotic medications may be used with caution to facilitate movement of stools to the rectum [10].

55.4.6 Bowel Irrigation

For both the UMN and LMN bowel, transanal irrigation is a viable option to supplement bowel program/bowel care. The unique enema system (Peristeen™, Navina™) which is comprised by a rectal balloon catheter and a pump, delivers pulsed irrigation to cleanse the rectum up to the sigmoid [10]. It has been demonstrated to be a safe and effective method to manage fecal loading and impactions [50, 55]. A large multi-site randomized controlled study showed that transanal irrigation improved constipation, incontinence, overall bowel function, total time for bowel care, gastrointestinal symptoms and quality of life in individuals with SCI compared to the regular bowel program [5, 55–57]. Succeeding studies revealed lower costs of care [5, 56]. reduced or discontinued use of medications [56, 58]. long term successful outcomes with continued use of the device, and resolution of symptoms [50, 55].

55.4.7 Surgical Treatment

55.4.7.1 Electrical Stimulation

Stimulation of anterior sacral roots S2, S3, and S4 by transrectal electric stimulation or more common to the urologist via a sacral neuromodulation (SNM) of the S3 nerve root alone from a surgically placed generator and lead identical to those used for urinary urgency/frequency (Interstim™ Medtronic Minneapolis, MN), urgency incontinence or non-obstructive urinary retention has been attempted for neurogenic bowel, albeit rarely [59, 60] with some modest efficacy. This SNM implant is FDA approved for fecal incontinence in the non-neurogenic patient [61]. with robust data and 87% having a positive response with the lead placement test phase (initial success) with incontinence episodes decreasing from 16 to 3 per week. Fifty two per cent of patients maintained continued efficacy long term over 7 years. More studies on this device in patients with neurological disease have studied the effect of SNM specifically on neurogenic bladder with good outcomes particularly in multiple sclerosis patients, and much less efficacy with spinal cord injury [62]. Anatomically stimulation of S2 tends to promote non peristaltic, low-level electrical impulses to the sacral plexus, influencing the anal canal, colon and pelvic floor musculature. Stimulation of S3 causes occasional high-pressure peristaltic waves, especially with repetitive stimulation; stimulation of S4 increases both rectal and anal tone; however, consistent changes in anal resting pressure and other manometric outcome measures have not been reported in the literature. Less invasive approaches such as percutaneous tibial nerve stimulation as is used for urgency or urgency incontinence of the bladder has been studied in non-neurogenic fecal incontinence [63] although is not FDA approved for this indication, it may be possible that this method could positively impact fecal incontinence in less severe neurological conditions with intact afferent nerves. Urologists need to be aware of these theoretical benefits for patients with NGB if performing the procedure for the bladder.

The sacral anterior root stimulator (Brindley stimulator) has been used in individuals with SCI to manage neurogenic bladder with electrodes surgically placed in the S2, S3 and S4 anterior nerve roots after sacral rhizotomy is performed which is controlled with an external device that delivers short, high voltage electrical stimulation to the bladder for emptying. Consequently, the sacral anterior root stimulator has produced good results for neurogenic bowels in case series studies [64, 65], by facilitating colonic motility and spontaneous bowel evacuation [4, 50, 66], reducing constipation and duration of bowel program [4, 5, 50, 65, 66], preventing autonomic dysreflexia during bowel care, enhancing quality of life [5, 50, 65] and reducing need for caregiver assistance [50, 67]. Fecal incontinence and quality of life were shown to improve with sacral nerve root stimulation in patients with cauda equina syndrome as well [50, 68]. Unfortunately, this device is no longer FDA approved and is susceptible to device breakage combined with the needs for an anterior approach to the sacral rhizotomy has limited its use.

55.4.7.2 Antegrade Continence Enema (ACE)

The options of the antegrade continence enema should be considered in clinical scenarios of failure of retrograde enemas due to prolonged bowel care time, recurrent fecal impactions, or poor or intermittent response to rectal medications to initiate bowel care. This is an alternative method of antegrade enema delivery that requires the surgical construction of a catheterizable appendicocecostomy stoma. The appendix

and right colon are mobilized through a small horizontal right lower quadrant incision and brought against the abdominal wall. The tip of the appendix is then amputated and the opening into the appendix lumen is modified into a catheterizable stoma on the lower right abdominal wall [69]. This procedure can now also be performed laparoscopically [70]. Alternatively in patients with extremely slow transit times the Macedo-Malone or left sided ACE (MACE or LACE) variation can be performed where a transverse strip of descending colon is tubularized into a catheterizable channel onto the lower left abdominal wall [71]. This stoma can be catheterized and infused with 200–600 mL of tap water to trigger a propulsive colonic peristalsis and defecation within 10–20 min. Bowel care can then be additionally facilitated with digital stimulation in the usual fashion. The ACE theoretically empties the entire colon and should only need to be performed every second day, whereas the left sided MACE clears mostly the transverse and descending colon requiring less time but clearing less of the colon and needs to be performed more frequently. These surgical procedures are easily performed at the time of another abdominal surgery for bladder reconstruction (augmentation cystoplasty, creation of continent catheterizable stoma) by the urologist with very little extra surgical time or morbidity which is why reconstructive bladder surgeons should be familiar with these techniques or combine efforts with a bowel surgeon who can.

55.4.7.3 Colostomy

Colostomies in this population are typically indicated in four general scenarios: (1) when conservative medical measures and training have failed; (2) when repetitive bowel impactions occur; (3) when pressure ulcers or other skin lesions occur that cannot be effectively healed because of frequent soiling, or (4) when intrinsic bowel deficits exist such as in Hirschsprung's disease, Chagas' disease, and colonic atresia. Colostomies have been demonstrated to be beneficial in multiple studies and systematic reviews in people with spinal cord injuries [5, 50, 72–75]. Colostomies promote ease in bowel care by simplifying and decreasing time spent on bowel management [50, 72, 74, 75], reduce bowel symptoms [50, 74] mitigate episodes of incontinence, lower rate of hospital admissions from GI problems [50, 74], encourage independence and raise quality of life [50, 74, 75]. Patients do report after their surgery regret in not having done their colostomy sooner [50, 72], therefore, a colostomy should be considered earlier in severe cases rather than pursuing futile conservative therapies for months and years. A sigmoid colostomy (left sided, more distal) is typically recommended to allow absorption of fluid, preserve hydration and have better formed stools [50, 76]. In a patient undergoing urinary incontinent diversion for intractable incontinence, poor bladder compliance or fistulas the urologist should consult with the patient's bowel management team since a colostomy may be simultaneously indicated, particularly with severe intractable dual incontinence or pressure ulcers. In this case a double barrel diversion can be performed with the urinary diversion utilizing an extra segment of large bowel after the colostomy is formed. This approach eliminates the need for any bowel anastomosis and is efficient [77].

55.5 Conclusion

Although to the treating urologist neurogenic bowel may seem to be a separate body system best left to the "specialist" significant shared morbidity, impact on social function and need for simultaneous conservation and surgical treatment makes it a condition that urologists not only need to be aware of but become an active member of their bowel care team. Treatments urologists provide to the bladder can benefit or harm bowel function and when embarking on surgery it does a great disservice to the patient to neglect simultaneously needed bowel procedures since the morbidity of combined approaches is far less than staged surgeries at different times.

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Sexual Dysfunction and Fertility in Neurogenic Lower Urinary Tract Dysfunction

56

Waleed Altaweel and Raouf Seyam

56.1 Introduction

In the 90s a better understanding of the pathophysiology of erectile dysfunction (ED) was formulating [1]. Simultaneously the magnitude and the correlates of male sexual dysfunction were getting in focus [2]. A few years later, oral phosphodiesterase type 5 inhibitors (PDE5i) came to use and along came the development of several objective assessment tools to gauge sexual dysfunction in men [3]. Parallel to these developments, lower urinary tract symptoms (LUTS) were under extensive investigations which resulted in a major shift in diagnosis and treatment. Not before long that the association of LUTS and male sexual dysfunction was clear [4]. Therapies that targeted both were tried [5, 6]. The female sexual dysfunction (FSD) finally reached focus and went along the path of development of objective assessment tools, identifying risk factors and looking at treatment options [7]. The association between a neurologic pathology and each facet of the genitourinary dysfunction is rampant in the literature, albite on a paired basis. The association between a neurologic pathology and either ED, orgasm, ejaculatory dysfunction, LUTS, fertility or FSD was repeatedly reported (Fig. 56.1). On the other hand, the association of LUTS on one hand and either male or female sexual dysfunction was a subject of many reports. There is a paucity of reporting of the association of the three conditions together whether in men or women. The purpose of this review is to shed light on citations that had a clear view of the presence of such association and how it was managed.

LUTS may result from a myriad of pathological conditions affecting the nervous system [8]. The prevalence of LUTS symptoms with the neuro-urological disease was summarized by the EAU guidelines [8]. A useful working scheme for discussion of sexual dysfunction and infertility in those patients is to consider the location of the neurological pathology. These include lesions above the spinal cord, spinal cord lesions, peripheral nerve lesions and multiple sclerosis (MS).

56.2 Methods

We searched Medline for all publications cited till August 2017 that included text words in the title or abstract on a neurologic disease, sexual dysfunction/infertility, and LUTS. We restricted the search to English language citations, involving only humans (Fig. 56.1). Using the search syntax, we excluded articles primarily dealing with non-neurogenic LUTS, those including an anatomical pathology that may have contributed to sexual dysfunction or LUTS, namely prostatectomy, cystectomy, stress incontinence, pelvic organ prolapse, and gynecological surgery and citations focusing on the association of PDE5i and optic neuropathy (Fig. 56.2). We excluded two sets of citations that were not relevant to our target publications. The first group included a neurological disease and sexual dysfunction/infertility but no report on LUTS. An exception to this exclusion were reports on patients with spinal cord lesions where we assumed that LUTS were present in 80–90% of cases [8]. The same assumption was not made for MS patients where the presence of LUTS is extremely variable. The second group included patients with sexual dysfunction/infertility and LUTS but no underlying neurological disease reported. Reports on pure stress incontinence were excluded.

56.3 Results

As of the 20th of Aug 2017, we found 256 PubMed citations associating neurogenic etiology, LUTS, and sexual dysfunction (Fig. 56.1). An additional search on SCI and

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_56

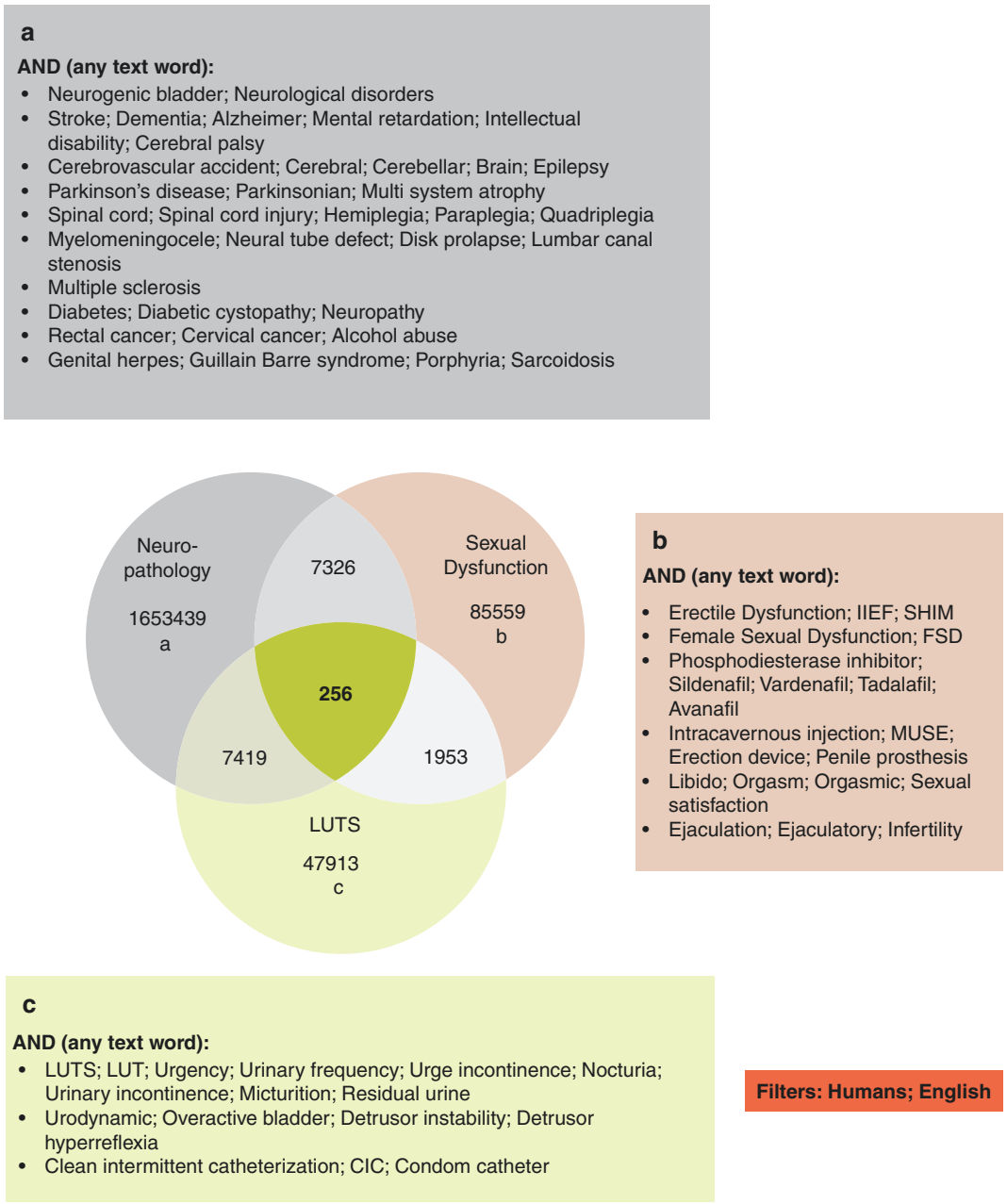

Fig. 56.1 PubMed search words. (**a**) Neurogenic disease, (**b**) sexual dysfunction, and (**c**) LUTS. The Venn diagram shows the number of citations retrieved in associations with the three conditions. Arabic numerals indicate the number of citations

sexual dysfunction yielded 882 citations (Fig. 56.2). Running the total of 1072 citations through our exclusion filter we ended up with 616 citations. The abstracts were reviewed and those that did not meet the search criteria were excluded. We selected 280 articles to include in this review. Information was collected from the abstracts and full manuscripts. A discussion of our main findings is given below.

56.3.1 Multiple Sclerosis

56.3.1.1 Prevalence of LUTS and Sexual Dysfunction

There is a significant association between MS, LUTS and sexual dysfunction reflected in studies of patients in different settings. In a population-based study of MS patients, the prevalence of bladder dysfunction or indwelling catheter was

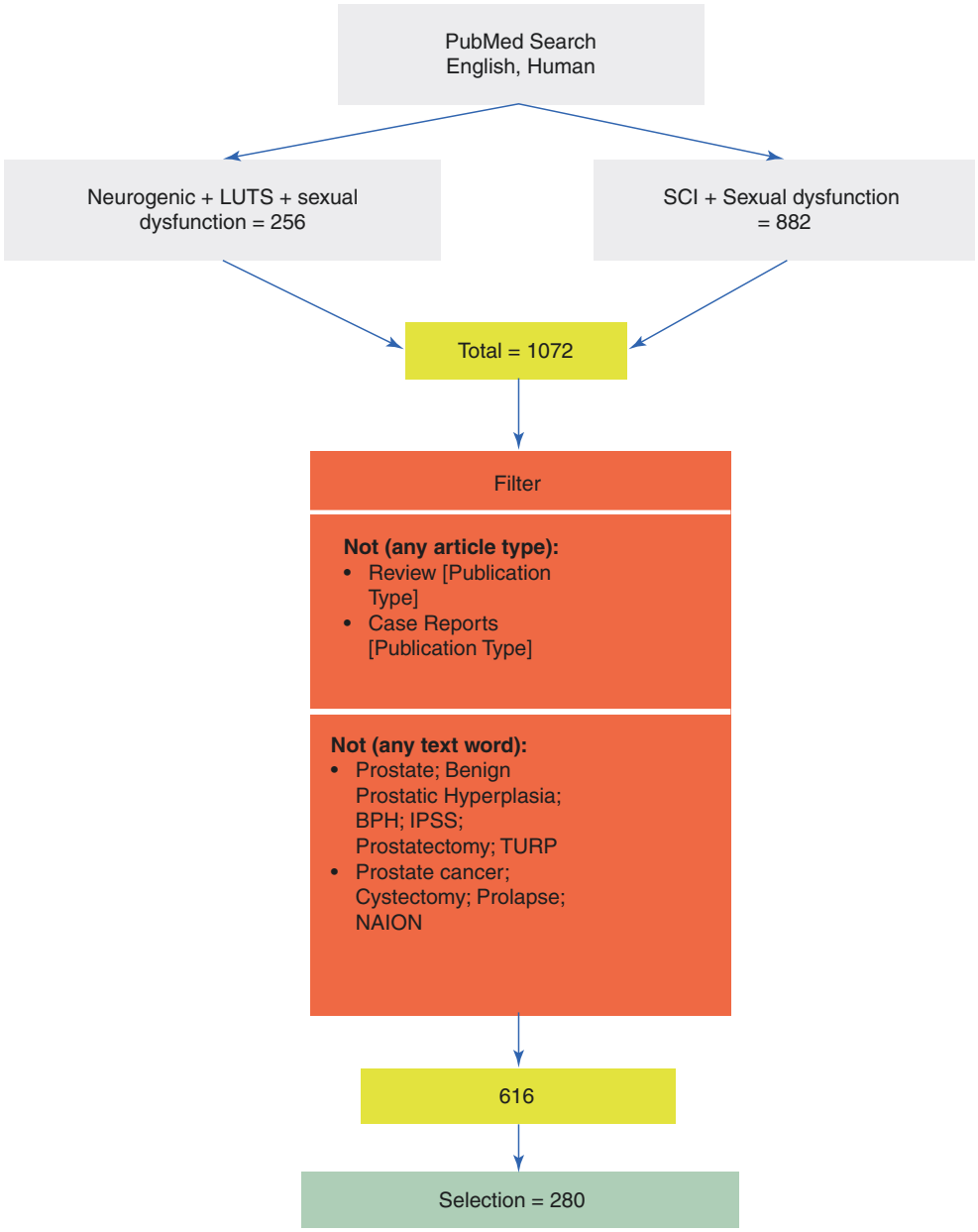

Fig. 56.2 A flow chart showing the inclusion of search on SCI and sexual dysfunction, application of exclusion filters and the citation selection. Arabic numerals indicate the number of citations

reported in 51.6% [9]. Deterioration of sexual activity was reported by 82% of men and 52% of women. A questionnaire of patients with MS, more than half of them were ambulatory without aid, found that sexual dysfunction affected 75% of men and 56% of women [10]. Spasticity and bladder dysfunction were associated with sexual dysfunction. In a comparison with patients having a chronic disease or healthy individuals, more than 70% of patients with MS reported sexual or sphincter dysfunction which was significantly higher than controls [11]. Another study involving patients referred for evaluation showed that 97% had symptoms of voiding dysfunction and 71% of men had sexual dysfunction [12]. Detrusor hyperreflexia and detrusor sphincter dyssynergia occurred in 76% and 50% respectively.

Longitudinal follow-up of patients with MS showed that many develop sexual and urinary dysfunction, yet with variable proportions relative to the duration of the disease. In a population-based cohort study of 209 MS patients who had the disease for 9–19 years, 57.5% reported bladder dysfunction and 51% sexual dysfunction [13]. Another cohort of patients was followed for 3–5 years and showed that nearly half suffered from the bladder and sexual dysfunction [14]. Other studies reported a higher incidence of bladder and sexual dysfunction. During a follow up of patients with MS

for 2 years, sexual dysfunction affected 70% and was associated with increased symptoms over time [15]. In another cohort study of men and women with MS followed for 6 years, the frequency of bladder dysfunction, mostly urgency, was high and increased with the duration of the disease to 71.4% for men and 66.7% for women [16]. Cross sectional and cohort studies showed that there was a significant correlation between bladder dysfunction and sexual dysfunction [14, 16, 17].

56.3.1.2 Nature of Dysfunction

Patients with MS reported different patterns of sexual dysfunction that were associated with urinary symptoms [18–20]. The patients reported a decrease in sexual activity and interest in sex, decreased genital sensation and difficulty achieving orgasm following the diagnosis of MS [18]. Men complained of ED and ejaculatory dysfunction [18, 21], while women had decreased vaginal lubrication and decreased, difficult or no orgasm [18, 19, 21, 22]. The impact of MS on female sexual dysfunction is variable. Women with MS reported bladder dysfunction in 61% but could enjoy sexual activity, arousal, and orgasm in 70% [23]. Strangely, higher urge incontinence was associated with higher level of orgasm. Whereas, women with advanced MS who had the disease for a median of 16.5 years had more common sexual dysfunction associated with urinary dysfunction (89.4%), affecting desire (59.6%), genital sensation (61.7%), lubrication (46.8%) and orgasm (51.1%) [20].

56.3.1.3 Mechanisms of Dysfunction and Correlations

Several factors may contribute to the association of MS, LUTS and sexual dysfunction. These may include neurological dysfunction, psychological factors, and physical disability. Common underlying neurological pathology may explain the association of sphincter dysfunction and sexual dysfunction [17]. The left dorsolateral pontine tegmentum is associated with ejaculation in men and orgasm in women [24]. The corresponding area on the right side is associated with micturition. Both areas send efferents to the parasympathetic pelvic nerves. The ventral pontine area sends somatic efferents to the pelvic floor muscles which cause contraction during ejaculation and orgasm. Pontine atrophy and MRI T1 lesion load were associated with sexual dysfunction in both genders [25]. In addition, detrusor overactivity was an independent predictor of ED and FSD [26]. Abnormal or absent pudendal cortical evoked potentials were associated with the complaint of difficulty or no orgasm in women [22], while decreased arousal score was associated with decreases vaginal lubrication [19]. A significant correlation was found between sexual dysfunction, lower limb symptoms and bladder symptoms in men but not in women [21]. ED with MS significantly correlated with lower limb pyramidal symptoms and bladder hyperreflexia [27].

Other underlying factors may play a role in the association of MS, LUTS and sexual dysfunction including physical disability [28, 29], fatigue [21], psychological factors and socioeconomic issues [17]. In patients affected by MS for <5 years, both more severe sexual dysfunction and bladder dysfunction were significantly associated with the physical disability; during longer follow up the association was significant only for more severe bladder dysfunction [29]. The relationship between the level of physical disability and bladder and sexual dysfunction was evaluated in a cross-sectional study [28]. With lower physical disability, 53% of patients with MS had sexual dysfunction and 44% had bladder dysfunction. In patients with higher disability scores, 86% had sexual dysfunction and 81% bladder dysfunction. In women, sexual dysfunction was significantly associated with all other MS disabilities but markedly with fatigue [21].

Sexual dysfunction in patients with MS correlated with symptoms of bladder dysfunction [30], however, this correlation was not universally apparent with urodynamic findings [25, 31, 32]. In patients with MS in remission and having LUTS, urodynamic findings were correlated with sexual dysfunction [32]. In men, ED correlated with lower bladder cytometric capacity, maximum detrusor pressure, and compliance, while in women there was no significant correlation between FSD and urodynamic variables [32]. In another study of men with MS who complained of sexual dysfunction, no significant correlation between urodynamic abnormalities and ED was found [31]. The results of this study might be interpreted with caution as most patients had no dysfunction found upon an objective assessment that involved nocturnal penile erection, response to visual erotic stimulation and penile vibratory stimulation (PVS).

56.3.1.4 Management of Combined Symptoms

Management of LUTS may have an impact of sexual symptoms in patients with MS and vice versa. In women with MS, treatment of overactive bladder (OAB) with onabotulinum toxin type A improved urinary symptoms, urodynamic parameters and sexual dysfunction in those who became continent [33]. Another study showed that pelvic floor muscle training for urinary dysfunction resulted in improvement of sexual function affecting arousal, lubrication, and satisfaction [34]. In men as well, treatment of ED had a positive impact on urinary symptoms. In young patients with MS, ED and neurogenic OAB dysfunction, a prospective study showed that treatment with tadalafil 5 mg daily dose resulted in a significant improvement of the International Index of Erectile Function (IIEF) score, the International Prostate Symptom Score (IPSS), OAB score, flow rate, residual volume and testosterone to estradiol ratio [35].

Sympathomimetics may help patients with MS have a better ejaculation. Midodrine reverses ejaculatory dysfunction in MS affected men [36]. The efficacy of midodrine in patients with anejaculation due to nerve lesions, which did not include patients with spinal cord injury (SCI), is slightly lower. In a study of such patients, 54.7% obtained antegrade, retrograde or mixed ejaculation after treatment with midodrine [36]. The most favorable results were associated with MS and the worst results with bilateral sympathectomy.

Counselling for patients with MS needs to incorporate sexual assessment. Although there is a clear association between urinary and sexual dysfunction in patients with MS, however, during clinic visits, patients were less frequently asked about sexual history probably leading to underestimation of sexual dysfunction [37].

56.3.2 Spinal Cord Injury

The following discussion assumes that all patients with SCI have urinary dysfunction. Few of the reviewed articles include non-traumatic lesions of the spinal cord.

56.3.2.1 Sexual Dysfunction: Comparison Between Men and Women

A cross-sectional community-based study revealed that sexual dysfunction is one of the most common comorbidities affecting patients with SCI [38]. In a large group of men and women who had a history of trauma, multivariate analysis showed that spinal cord injury was associated with the largest relative risk of 3.7 of developing sexual dysfunction; the risk was the highest among other independent risk factors including age, diabetes, baseline health status and pelvic fracture [39]. By 6 months after initial hospital rehabilitation, patients achieve a stable level of the change in sexual interest and activity [40]. Recently, more attention was directed to the assessment of sexual dysfunction associated with SCI. The international SCI society developed basic data sets designed to collect data on sexual dysfunction in both men and women before and after their injury [41, 42]. The questionnaires go beyond diagnosis into the assessment of the interest of patients to pursue management of sexual dysfunction.

There are differences between men and women in the proportion of sexual dysfunction and coping with it following SCI. A cross sectional study of patients with SCI for more than 10 years reported that 69% of women were satisfied with sexual life and 22% gave birth after injury [43]. Of men, 75% could get an erection and 44 could ejaculate. Men used aids for erection in 35% of cases and for ejaculation in 56%. Patients who had better sexual function were younger. Lower satisfaction of sexual life was associated with bladder dysfunction, bowel dysfunction, pressure ulcers, spasticity, and pain. Dissatisfaction with sexual dysfunction is more in men with traumatic SCI than in women and is related to urinary leakage and pain [44]. An Australian study of self-reported sexual dysfunction in patients after SCI showed that 76% had a sexual dysfunction related to the injury [45]. Men had more prevalent dysfunction in orgasm, psychogenic genital function and reflex genital function than women. Only 3% of men had a normal ejaculation. Women with myelomeningocele had the least dissatisfaction with sexual function [44].

The level and extent of the lesions involving the spinal cord impact sexual function in both sexes. Men with SCI and lesions above S2-S4 had a mean value for rigidity during nocturnal penile tumescence testing of 89% and 83% for partial and complete lesions respectively [46]. Patients with complete sacral lesions had a mean rigidity of 46%. Patients with a combined sacral and thoracolumbar lesion had no erections. In patients with spina bifida, 24% of men and women were sexually active [47]. The most significant factor affecting sexual function was the level of the lesion with the caudal site having the least effect. Factors that did not impact the sexual function were the degree of urinary incontinence, the extent of physical disability and gender [47]. Adult patients with spina bifida reported FSD in 89% and severe ED in 59% [48]. Erectile function was better in men with lower spinal lesions.

The etiology of SCI may affect the level of sexual dysfunction in men and women. Patients who had SCI due to attempted suicide had more pre-existing sexual dysfunction and continued to have the dysfunction after the injury in comparison to SCI patients of other causes [49].

56.3.2.2 Sexual Dysfunction in Men

SCI leads to a significant portion of men having sexual dysfunction. Age, the duration of injury and extent of impairment affects the degree of sexual dysfunction and how patients cope with it. All male veterans with SCI of an average duration of more than 20 years had ED; 27% of them had a severe degree [50]. In a study of patients with spinal cord injury on clean intermittent catheterization (CIC), 67% did not have sexual activity in the previous 6 months, while almost all the remaining patients had a poor IIEF score [51]. A study of younger men with a mean age of 35.2 years reported moderate to severe ED in 87.3% [52]. Another study involving young men with a post-injury duration of 4.6 years revealed that independent risk factors affecting erectile function were age, the level of education, the degree of impairment, anxiety, religious coping and duration of injury [53]. Older patients with SCI report more frequent ED than their younger counterparts [54]. Older patients, however, resort to sexual intimacy more than intercourse relative to the younger patients, although the quality of life scores were high for both groups. Men reported decreased sexual activity, and sexual satisfaction and increased interest in an

alternative non-penetrative sexual activity [55]. The patients reported sexual adjustment difficulties in 27% and relationship difficulties in 74%. ED rather than urinary and bowel dysfunction was the major factor contributing to depression and psychological anxiety in patients with SCI [56]. Engagement in sexual activity (65%) was associated with a longer duration of SCI more than 20 years and having sexual rehabilitation [57]. Most sexually active men (62.2%), however, were not satisfied with their sex life and this correlated with a lower level of education.

There is an agreement that erection, ejaculation, and orgasm are affected by SCI but different opinion exists on the effect on desire. In one study, following SCI, men reported decreased desire and perceived partner desire [55]. Another study, however, reported that SCI does not affect sexual desire in men but significantly negatively affects arousal and orgasm [58]. A total of 86% of men experienced sexual desire and 65% felt orgasm but weaker than before the injury [59]. A low testosterone level was a risk factor for low desire in men with chronic SCI [60]. A lower testosterone level was independently associated with lower physical activity and higher BMI. The impairment of sexual desire, however, may be the most important factor affecting satisfaction and quality of relationship than other dysfunctions. In a study of SCI men in a steady sexual relationship, there was a significant positive correlation between sexual satisfaction with partner satisfaction, quality of relationship and sexual desire while no significant association was found with erectile function, genital sensation or orgasmic capacity [61].

Men with SCI are less likely to achieve orgasm compared to controls [62]. The orgasmic dysfunction is associated more with complete SCI and sacral segment lesions. Interestingly, there was a discordance between the occurrence of orgasm and ejaculation. Another study, however, found that patients perceived orgasm with ejaculation [63]. Self-ejaculation could be reached in 91% of patients by using natural stimulation (30%), PVS alone (49%) or with midodrine (12%) premedication. Contrary to the commonly reported difficulty of orgasm in SCI, de novo premature ejaculation was reported in some patients suddenly after injury at level T12-L1 [64]. One study reported that most men with lumbosacral lesions affecting L5-S4 maintained a natural albeit commonly premature or spontaneous ejaculation [65]. Autonomic hyperreflexia may develop in association with orgasm [66].

Men with sexual dysfunction following SCI have different pathophysiology compared to men with sexual dysfunction not associated with SCI [67]. As expected, tests for the integrity of neuronal pathways and ejaculation were impaired in patients with SCI. More vascular and hormonal risk factors might be predominating in other patients. Those without SCI were older, had more prevalent ED, premature ejaculation, anxiety, depression and had a lower desire and less cavernous artery peak systolic pressure [67]. Men with SCI and sexual dysfunction may have a better social quality of life than those without SCI reflecting a better adaptation related to a lower level of depression and anxiety [68].

An interesting study showed that repeated PVS to induce ejaculation in men with SCI, led to a significant increase of bladder capacity at leak point from a median 190–293 mL after 4 weeks of treatment [69]. This finding might be explained by the shared neural pathways between the penis and bladder and that suppression or stimulation of one may affect the other. A shared loss of pathways affecting the parasympathetic pelvic nerves and the somatic bulbocavernosus reflex arc resulted in both the development of detrusor areflexia and loss of reflexogenic erection [70]. Further benefits of PVS in men with SCI was a significant relief in spasticity [71, 72].

Other genitourinary comorbidities were reported in association with SCI. Non-ischemic priapism developed after acute SCI but usually resolved with conservative management with no long-term negative consequences [73]. Corpus cavernous fibrosis developed following SCI and upregulation of TGF-β1 and its signaling pathway were implicated [74]. Finally, epididymo-orchitis developed more frequently in SCI patients on CIC [75]. As high as 38.5% epididymo-orchitis was reported in SCI patients [76]. There was no clear association with UTI or a urethral pathology.

Non-traumatic conditions affecting the spinal cord were associated with sexual dysfunction. Men with myelomeningocele engage in sexual activity later in their life and 75% had lower than normal IIEF score [77]. Successful surgery for cervical spondylotic myelopathy resulted in neurologic recovery and a significant improvement of erectile function [78].

56.3.2.3 Sexual Dysfunction in Women

SCI is commonly associated FSD that affects as high as 82–88% of women in different parts of the world [79, 80]. Contributing factors leading to sexual dysfunction included difficulty in positioning during sexual activity, impaired vaginal lubrication, spasm and autonomic dysreflexia [81]. The frequency and ability to reach orgasm decreased compared to activity prior to the injury [82]. In response to audiovisual erotic and manual genital stimulation, only 50% of women with SCI could reach an orgasm compared to 100% of able-bodied women [83]. Patients had a longer latency to orgasm and responded least when lesions affected the sacral spinal segments. The vagus nerve may be an alternative route to spinal pathways conveying afferent stimuli leading to orgasm in women with complete SCI at or above T10 [84].

Although SCI significantly impairs arousal, orgasm, genital sensation and satisfaction, yet a clear majority of women remain sexually active. Up to 80% of women remain sexually active after SCI [85]. In the presence of arousal

dysfunction, most women with SCI reported engagement in sexual activity [81]. In one study 392 out of 532 respondents reported having sex, yet had less satisfaction than before the injury [86]. In another study 62% women with SCI for an average of 10 years and a mean age of 40 years, engaged in the sexual activity regularly after injury [82]. Two-thirds of the patients were satisfied with their sex life. In a study of Turkish women with SCI >6 m, all of them suffered from FSD, one-third had regular sexual intercourse [87]. The only factors that determined sexual activity in SCI women in southern Spain were having a partner and genital sensation [88]. When compared to carefully matched controls, women with severe cervical SCI had less sexual activity, however, there was no significant difference in sexual desire, emotional quality or satisfaction [89].

Other non-traumatic conditions affecting the spinal cord may lead to sexual dysfunction. Young women 28 ± 6 years old who had spina bifida or myelomeningocele reported poor sexual function [90]. Urinary incontinence was the main factor leading to sexual dysfunction.

56.3.2.4 Treatment of SCI Associated Sexual Dysfunction

The sequence of management of ED in SCI patients is similar to other etiologies, including identification and correction of reversible risk factors, oral PDE5i, vasoactive intracavernous or intraurethral injection vacuum erection device (VED) and penile prostheses, all resulting in increased sexual activity [91–93]. The management, however, may differ in drug dosage, outcome, medication adverse events and surgical complications.

A recent systematic review and meta-analysis of six studies that used oral PDE5i to treat ED in patients with SCI found that the treatment is efficacious and well tolerated although side effects were significantly more reported than in the placebo groups [93]. Early studies showed that treatment with sildenafil in SCI patients is effective and well tolerated [94]. Sildenafil is effective in the treatment of ED in SCI patients of various etiologies and levels [95]. The treatment was particularly effective in patients with a partial lesion, lesions above T12, in the presence of residual erection, and the presence of either reflexogenic or psychogenic erection denoting a preserved sacral or thoracolumbar autonomic innervation [96–98]. While sildenafil was effective in the treatment of patients with UMNL in 82% vs. 25% in placebo treated patients, there was no significant effect of treatment in LMNL patients [99]. Sildenafil treatment is associated with significant improvement of the quality of life, satisfaction with sex life, sexual relationship and concerns about ED [100]. The efficacy of sildenafil was comparable to papaverine intracavernous injection (ICI) for the treatment of ED in paraplegia of recent onset [101].

Hypotension due to PDE5i might be a concern in some SCI patients. Measured decrease in blood pressure was associated with sildenafil treatment in men with SCI above T5 and complete lesions, although without clinical consequences [102]. Patients with higher spasticity scores were less likely to develop hypotension. In another clinical trial, however, sildenafil treatment caused hypotension and dizziness in patients with cervical lesions but not with thoracic lesions requiring caution in prescription in the former group [103]. Taking advantage of this hypotensive effect, an attempt to prevent hypertensive autonomic dysreflexia associated with PVS, sildenafil premedication was used but showed no benefit [104].

Other oral PDE5i showed similar efficacy and tolerability to sildenafil in other studies and flexible dosage clinical trials [105]. Tadalafil was effective and well tolerated in the treatment of ED in patients with SCI [106, 107]. A clinical trial showed that tadalafil has the advantage of a longer duration of action than sildenafil in SCI patients [108]. Vardenafil improved erection, ejaculation, and self-confidence in patients with SCI [109, 110]. The higher 20 mg dose was more efficacious than the 10 mg dose [111].

Treatment with PDE5i may have beneficial effects on lower urinary tract function in SCI patients. Single dose tadalafil improved urodynamic parameters in patients with supra sacral SCI [112]. In addition, a single dose vardenafil resulted in a significant improvement of urodynamic parameters in SCI including a decrease in detrusor pressure and overactivity and increase in cystometric capacity [113].

Several studies reported treatment with ICI of vasoactive medications for ED in SCI patients. Patients were successfully treated but 16.1% developed priapism [114]. ICI with low dose papaverine (12 mg or less) was effective and well tolerated in 56% of patients with SCI and ED [115]. Almost all patients who used papaverine ICI up to 60 mg obtained a rigid erection sufficient for penetration [116]. Only 3% had priapism with 1% requiring treatment and 1% developing penile fibrosis.

Prostaglandin E1 is more desirable as it causes less fibrosis and priapism. ICI of prostaglandin E1 was effective and associated with no priapism in patients with SCI and ED using a mean dose of 6.2 μg [117]. A large group of patients on PGE1 ICI treatment had 1.3% priapism [118]. Interestingly, all patients were successfully treated with oral midodrine. To salvage patients who do not respond to single medications, a mixture of vasoactive drugs is usually used. ICI with a bimix of PGE1 and papaverine was associated with erectile response in 76% of SCI patients [119]. Three months follow up showed high adherence to treatment and satisfaction rate.

Patients who dislike needle injections may be offered intraurethral vasoactive medication. Intraurethral prostaglandin E1 (MUSE) was effective in the treatment of SCI ED

patients [120]. The treatment efficacy was related to the 1000 μg does, was associated with hypotension unless a constriction ring was used and was less effective and less satisfactory to patients than intracavernosal injections.

Mechanical devices might offer an alternative, simple treatment for some patients and provide adequate erection for penetration, yet with some limitations. VED was effective and well tolerated in patients with SCI [121]. The 6 months satisfaction rate, however, dropped to 41% and 45% for patients and partners respectively. Few SCI patients using VED developed subcutaneous bleeding and penile ischemia [114].

Penile prosthesis implantation can be used to serve a dual purpose of treating erectile dysfunction and facilitating urinary management [122–127]. Besides providing penile rigidity for intercourse, the prosthesis prevents penis retraction, keeping the condom catheter in place, and increasing accessibility to the urethral meatus easing self-catheterization. Reported patient satisfaction was high for both goals with the use of penile prostheses of different types. Following non-inflatable penile prosthesis implantation, patient satisfaction for urinary management was reported in 93% and for sexual dysfunction in 64% [125]. Semirigid penile prosthesis implantation was reported solely to facilitate maintaining a condom catheter on the penis [128]. SCI patients who previously suffered from condom catheter loss due to retracted penis reported post-implantation an increased mobility and self-esteem and 80% did not have accidents of condom loss [128]. In addition, 68% of patients used the implant for sex and reported wife satisfaction. Non-inflatable silicone penile prosthesis implantation was associated with 86% satisfaction of urinary management and 41% improvement of sexual function [122]. Malleable penile prosthesis implantation resulted in an overall satisfaction in 79.2% of patients [127]. An early experience using mostly malleable and few inflatable prosthesis reported that 72.7% patients became sexually active [124]. A study of 245 patients with different neurogenic lesions who had different types of a penile prosthesis implanted reported a successful management of the urinary problem and ED in 90.3% and 82.6% patients respectively [126].

There are significant complications associated with penile prosthesis implantation in patients with SCI. Paraplegia was one of the significant risk factors of penile prosthesis infection [129]. In one report, the overall prosthesis infection rate was 2.2% but reached 15% in SCI patients [130]. Non-inflatable silicone penile prosthesis was removed due to infection, pain or migration in 12.1% of patients [122]. Similarly, the complication rate for non-inflatable penile prosthesis implantation reached 13.3% in one study which included extrusion of the prosthesis, and surgical removal because of pain, the difficulty of catheterization and infection [125]. The reported erosion rate for semi-rigid prosthesis was 33% in earlier studies [131]. The reported patient complication rate for the malleable penile prosthesis is 16.7%, including wound infection in 8.3% and removal of prosthesis because of infection in 4.2% erosion in 4.2% and pain or deformity in 4.2% [127]. The semi-rigid prosthesis was associated with 19.5% extrusion, surgical removal or unsuccessful implanting [123]. One study using mostly malleable and few inflatable prosthesis reported a high overall complication rate reaching 18.2% [124]. The use of inflatable prosthesis was associated with fewer non-mechanical complications [132]. One study compared the results of the implantation of different types of penile prosthesis in SCI patients. At a mean follow-up of 7.2 years, 43 revisions were needed and the infection rate was 5%. Perforation was highest for the semi-rigid prosthesis affecting 18.1% of patients, followed by the self-contained inflating prosthesis affecting 2.4%, while none of the 3-piece inflatable prosthesis patients had any perforation [126]. In the absence of a controlled clinical trial, it is not known whether the rate of complications is different for penile prosthesis implantation among patients with SCI and those with other causes of ED.

Some reports showed that few patients with partial SCI treated by neuromodulation had improvement of erection [133]. Patients with SCI who failed dorsal sacral nerve stimulation implants may benefit from a ventral approach targeting the sacral nerve roots through a transpersonal laparoscopic approach to improve visceral function [134]. A couple of men treated in this way improved their erectile function as well. A high success rate of erection, in addition to the improvement of urinary function, was reported. Sacral anterior root electric stimulator implantation for patients with complete SCI has resulted in bladder control, reducing residual urine, increasing capacity and continence [135]. Meanwhile 87.9% men could obtain a rigid erection using the stimulator.

There is a paucity of reports on the treatment of FSD in SCI women. Early reports suggested that treatment of SCI women with oral PDE5i may improve subjective arousal [136]. In later studies, however, sildenafil was not effective in the treatment of sexual dysfunction in these women [137].

For both men and women, there is a need to improve sexual counseling and education during rehabilitation for patients with traumatic and non-traumatic spinal cord dysfunction [138, 139]. Many women with SCI complain that caregivers did not initiate a discussion on sexual dysfunction during management. One study reported that almost all patients during rehabilitation did not receive any information on sexual health or pregnancy and were welcoming if caregivers were to initiate discussion on the subject [87]. Another study reported that 77% of women received inadequate information on the subject from their doctors [82].

56.3.2.5 Infertility

Ejaculation and Sperm Retrieval

Ejaculation success, by a natural or assisted means, depends on the level of SCI and whether it is complete or incomplete. In a meta-analysis of 45 studies of ejaculation in SCI patients, masturbation or coitus resulted in ejaculation in 11.8% patients having complete SCI and 33.2% with a partial injury [140]. Premedication with acetylcholine inhibitors increased successful ejaculation to 54.7% and 78.1% respectively [140]. PVS induced ejaculation in 47.4% and 52.8% of patients with complete or partial SCI. No patient with complete lesions of the sympathetic centers or the sacral parasympathetic and somatic centers could ejaculate in response to PVS. Isolated lesions were associated with better results. Few patients could ejaculate following acetylcholine inhibitors and masturbation when they had only sympathetic center lesions at T12-L2, whereas 31% of patients with only S2-S4 lesions could ejaculate. PVS in patients with SCI affecting cervical or higher thoracic segments is commonly associated with autonomic dysreflexia resulting in elevated arterial blood pressure and ECG abnormalities [141]. Almost all patients with tetraplegia had autonomic dysreflexia during vibratory or self-stimulation leading to ejaculation [142]. Only patients with incomplete tetraplegia could feel the symptoms of autonomic dysreflexia. Prazosin premedication was shown in a clinical trial to ameliorate the blood pressure surge without affecting baseline pressure [143]. A dual pad penile vibrator was recently described with a high ejaculation success rate, however, its advantage needs to be shown in a controlled study [144].

Nonsurgical sperm retrieval is frequently successful after SCI. In one study, sperms were retrieved by masturbation in 9%, and by PVS in 86% of patients with lesions above spinal segment T10 [145]. With salvage electroejaculation, the total retrieval rate was 97% [145]. High amplitude PVS causes significantly more SCI men to ejaculate (55% vs. 40%) and larger semen volume [146]. The reproducibility of the ejaculation is 100% with no difference between the two amplitudes regarding sperm quality. Patients who fail sperm retrieval by high amplitude vibratory stimulation may still produce ejaculated semen after utilization of dual penile vibrator technique [147]. The persistence of bulbocavernosus reflex and hip flexor reflex predicted the success of PVS to produce successful ejaculation [148]. Galaninergic neurons located at L2-L5 spinal segments are involved in the generation of ejaculation [149]. SCI affecting these segments results in failure of PVS to induce ejaculation.

Premedication with the sympathomimetic midodrine may improve ejaculation and orgasm in patients with SCI. Using various stimulatory methods with or without midodrine, ejaculation could be achieved in 89% of men with SCI [150]. A blood pressure increase of 11–35 mmHg was associated with only successful ejaculation. The treatment of SCI with midodrine converted anejaculation on PVS to antegrade or retrograde ejaculation in 65% of patients [151]. An orgasm was perceived by patients in 9% prior and 59% after midodrine treatment. Factors that lead to successful ejaculation/orgasm were upper motor neuron lesions, incomplete lesions, intact sacral cord and intact T10-L2 spinal cord. Intense autonomic dysreflexia developed mainly in tetraplegic patients.

In contrast, a recent placebo controlled trial of midodrine flexible dose treatment and single PVS could not demonstrate significant advantage towards antegrade ejaculation in patients with SCI lesions above T10 and anejaculation [152].

Electroejaculation is a last resort for sperm retrieval in patients with SCI. When it fails, different techniques have been used to produce ejaculation before a surgical means is contemplated. In a large group of SCI patients, azoospermia following vibratory penile stimulation or electroejaculation were subjected to repeat electroejaculation before proceeding to surgical retrieval [153]. A second VPS failed to produce any sperm whereas a subsequent electroejaculation produced sperm in 9 out of 26 patients. The overall prevalence of azoospermia after all trials was 7%. Using interrupted delivery electroejaculation rather than continuous delivery resulted in a significantly larger volume of antegrade ejaculation [154]. Both external and internal sphincters contract in response to electroejaculation just prior to ejaculation [155]. An interruption of electric stimulation at this point will allow relaxation of the external sphincter to permit antegrade ejaculation. Patients with myelomeningocele were particularly difficult to ejaculate with PVS and required electroejaculation under general anesthesia with some success [156].

An interesting finding in 27% of SCI who underwent sperm retrieval was the presence of a brown colored semen at least in one sample [157]. In nearly half of the colored semen, blood or blood pigments were found, however, there was no difference in sperm motility or concentration compared to non-colored samples. Finally, SCI patients who failed repeated electroejaculation or vibratory stimulation were managed by Testicular Sperm Aspiration/Testicular Sperm Extraction [158]. Sperm retrieval was high (90%) and live birth rate outcome for couples was significant (63%).

Semen Quality

Many studies showed that ejaculated sperms retrieved by different methods of stimulation in SCI patients have normal concentration, but decreased motility and vitality [159]. Ejaculated sperm by masturbation had higher motility than that obtained by PVS or electroejaculation [160]. Interestingly, sperm motility was better in patients with lower scrotal temperature [159]. Repeated ejaculation with PVS was associated with significantly improved sperm

morphology, forward progression but not with motility [161]. Another study, however, did not find any improvement in semen quality after repeated PVS [162]. PVS may produce antegrade or retrograde ejaculation. There was no significant difference in sperm concentration and quality between antegrade and retrograde samples [163].

Using rectal probe electrostimulation, 87% of patients with SCI had an antegrade ejaculation [164]. The semen quality showed suboptimal motility. The success rate was lower in patients with lower motor neuron lesions. Poor sperm quality might be partially related to urinary tract infection and the method of bladder drainage [165]. As patients emerged from spinal shock, the quality of sperms obtained by electroejaculation was significantly better than subsequent samples as the duration of SCI increased [166]. This observation led to the suggestion that cryopreservation should be carried out as soon as possible following SCI. As with PVS repeated electroejaculation may impact the quality of sperms. In one study, daily four repeated consecutive electroejaculation was associated with improving semen parameters [167]. A comparison between single and repeated electroejaculation confirmed that the later improved of semen qualities and significantly increased the pregnancy rate after ICSI [168].

The method of bladder management impacts the quality of sperm in SCI patients [169]. Patients who drained their bladders with CIC, a suprapubic catheter or an indwelling urethral catheter had better semen quality than those who voided by reflex or straining. Botulinum bladder injection affected semen quality. Patients with SCI and complete lesion affecting C5-T6 region who were injected had their semen evaluated before and after the treatment [170]. As a result, retrograde ejaculation increased with a decrease in semen volume, however, the quality of semen in terms of motility, vitality, and culture improved.

Most of SCI patients have poor quality semen. Interestingly, some patients produce semen with the normal quality compared to controls. Factors associated with a normal quality sperm retrieval were incomplete SCI lesions and ability to produce semen samples by masturbation [171]. Many studies investigated possible mechanisms leading to suboptimal sperm quality in SCI versus able-bodied men. The factors found in semen included elevated seminal reactive oxygen species levels [172, 173], poor quality sperms stored in the seminal vesicles [174], sperm exposure to seminal and prostatic fluid [175], ultrastructural degenerative changes [176] higher sperm DNA damage [177], impaired chromatin condensation, increased apoptosis and suboptimal DNA integrity [178], lower seminal PSA level [179, 180], low uridine concentration [181], lower seminal citrate concentration [182], lower acrosin activity and hyaluronic acid binding [183], and lower seminal zinc levels [184].

Other semen abnormalities implicated an inflammatory process causing poor semen quality, including higher total seminal white cell count, neutrophils and macrophages [185], higher inflammatory cytokines secreted by TH1 effector cells [186], higher platelet-activating factor acetylhydrolase activity [187] and an abnormal seminal plasma protein profile [188]. A proteomic study of seminal plasma indicated that sperm quality deterioration in SCI patients as compared to controls might be linked to nonbacterial induced hyperactivity of the immune system and metabolic prostatic dysfunction affecting ATP turnover [189]. Interestingly, interference with the inflammasome function by antibody blockade resulted in improved sperm motility in SCI patients [190].

DNA fragmentation and chromosomal aneuploidy are higher in sperms of infertile SCI patients while mitochondrial activity is lower compared to controls [191–193]. The method of collection, vibratory stimulation or electroejaculation did not significantly affect DNA fragmentation [191].

Other mechanisms may contribute to decreased motility and vitality of sperms of SCI patient. In one study evaluating the resistive index of testicular arteries, it was shown that testicular volume was lower and the testicular resistive index was higher in SCI compared to able bodied men [194]. In another study, serum inhibin B and testosterone were significantly lower than in controls [195]. Finally, susceptibility to bacterial infection may negatively affect sperm production by various mechanisms. One study showed that patients with anorectal malformation and neurogenic bladder were at risk of developing epididymitis [196].

Prostatic urethral sperm retrieval showed better quality of semen compared to bladder samples in SCI patient [197]. The better sperm concentration and motility of prostatic sperm were used for cryopreservation and may be considered in sperm retrieval in SCI patients. Cryopreservation negatively affects the quality of sperm, mitochondrial function, and DNA fragmentation but is not particularly more innocuous to semen from SCI patients as compared to controls [198]. Long term cryopreservation of sperm >3 years was associated with a significant impairment of motility and vitality and was not recommended for patients with SCI [199].

Assisted Reproduction

A systematic review published in 2005, reported that successful ejaculation was achieved in more than 95% of patients [200]. The pregnancy rate was 51% and live birth rate 41%. A variety of techniques were used to help men with anejaculation and SCI and their spouses to achieve pregnancy [201]. Nonsurgical methods of sperm retrieval included PVS and electroejaculation. Assisted reproduction techniques (ART) included intravaginal insemination, intrauterine insemination and in-vitro fertilization (IVF)/

intracytoplasmic sperm injection (ICSI) [201, 202]. The overall pregnancy rate per couple was 55%, pregnancy per cycle 18% and live birth rate 45.2% [201], and 70% pregnancy per couple using intravaginal insemination and 10/18 for other ART techniques [202]. Both the technique of sperm retrieval and method of fertilization affected the outcome. In selected patients, home intravaginal insemination and intrauterine insemination resulted in 37.8% and 24.6% pregnancy rate respectively [203]. Home self-intravaginal insemination with PVS resulting in antegrade ejaculation had an excellent outcome of 43% pregnancy and 73/140 live birth rates when patients had adequate sperm motility and healthy female partners [204]. Intravaginal insemination at home with PVS sperm resulted in a pregnancy rate per cycle of 22%. A lower rate of 5% was reported for electroejaculation sperm. Intrauterine insemination with electroejaculation improved the results to 30%. IVF/ICSI resulted in 19% pregnancy per cycle [201]. Better results for electroejaculation were reported elsewhere. Rectal probe electroejaculation was successful in 99% of SCI patients yielding sperms in 88% and couple pregnancy rate with ART of 70% [205]. A more recent study reported live birth rate of 36% [206].

The outcome of nonsurgical versus surgical retrieval of sperms was compared in couples of SCI men. Nonsurgical retrieval resulted in 63 pregnancies in 37 couples, whereas surgical retrieval of sperms from 27 patients resulted in 10 pregnancies [207]. The highest success rate of ART was reported with ICSI [208]. Intracorporal insemination or extracorporeal fertilization techniques resulted in a pregnancy rate of 46% per couple and the take-home baby of 46% [208].

Few studies compared outcomes of ART between SCI and other infertile patients. ICSI outcome was compared between SCI with anejaculation and patients with male factor infertility having severe oligozoospermia [209]. The reported fertilization rate was similar. However, pregnancy rate per cycle and per couple was significantly lower for SCI patients utilizing electroejaculation sperms compared to the control group. Yet pregnancy rate per couple for SCI patients was 29%. In contrast, another study comparing electroejaculation and ICSI outcomes between patients with psychogenic anejaculation and SCI reported superior fertilization for the SCI [210]. All other outcomes of implantation, pregnancy, and delivery rates were comparable. These findings were repeatedly reported by other studies. One study reported that pregnancy rates in couples with SCI and couples with obstructive azoospermia were similar at 68% each [211], and in a retrospective study of IVF/ICSI in men with and without SCI, reported pregnancy and live birth rates were similar [212]. There was no difference regarding success rates among methods of sperm retrieval by vibratory stimulation or electroejaculation.

56.3.3 Peripheral Nerves

Peripheral nerve lesions of medical or surgical etiology may lead to both urinary and sexual dysfunction in men and women. Diabetic neuropathy is a significant risk factor for both dysfunctions and is discussed below. However, peripheral and autonomic neuropathy in nondiabetic women with FSD were more commonly reported compared to controls [213].

Surgical injury of the pelvic autonomic nerve plexus is common following radical cystectomy and radical prostatectomy. Yet urinary dysfunction in those patients is more profoundly related to the structural alteration of the urinary tract anatomy and is not the subject of this review. Similarly, surgery for pelvic organ prolapse in women is not discussed because of difficulty to separate neurological from the anatomical dysfunction that follows. Very few reports were found on radical hysterectomy that included a report on both urinary and sexual function. Treatment of cervical cancer without brachytherapy resulted in vaginal dryness and dyspareunia at 1-year follow-up but no urinary dysfunction [214].

One surgical procedure that was frequently reported causing both sexual and urinary dysfunction was for excision of rectal cancer. Resection of rectal cancer affects urinary and sexual function variably according to the technique used, the extent of surgery, nerve preservation and the addition of chemotherapy or radiotherapy. Low anterior resection for rectal cancer with and without preoperative radiation was associated with 7% urinary incontinence, 69% male sexual dysfunction and 18% FSD [215]. More extensive surgery is followed by genitourinary complications that affect the quality of life of patients. Abdominoperineal resection and anterior resection of rectal cancer were associated with urinary incontinence and male sexual dysfunction that become worse at 1-year follow-up [216]. Nerve preservation of the pelvic autonomic plexus during resection for rectal cancer may reduce the complications of urinary incontinence, ED, and ejaculatory dysfunction [217, 218].

Resection of primary rectal cancer with total mesorectal excision (TME) had a favorable outcome on bladder function but not on sexual function [219]. However, the frequency of bladder and sexual dysfunction after TME was low [220]. The preservation of pelvic nerve plexus during TME is associated with preservation of both urinary and sexual function [221, 222]. The addition of lymph node dissection and not using a nerve-sparing technique resulted in a significant deterioration of sexual function and nocturnal penile tumescence at 1-year follow-up [222]. To facilitate identification and preservation of parasympathetic pelvic nerves, electrical nerve stimulation and monitoring of bladder contraction during TME were reported and prevented postoperative ED [223].

Preoperative radiotherapy for rectal cancer was associated with significant genitourinary complications affecting both men and women. Men developed ejaculatory dysfunction that was associated with preoperative radiotherapy [216]. In women, voiding difficulty and sexual dysfunction were significantly associated with preoperative radiotherapy [224]. Follow up showed that 77% had urgency, 63% incontinence, 72% vaginal dryness, 53% dyspareunia, 29% reduced vaginal size and 69% decreased sexual desire [224].

There are different views on the impact of laparoscopic surgery for rectal cancer on genitourinary complications. In elderly men, laparoscopic anterior rectal resection with TME had a minimal insignificant effect on the genito-urinary function with an incidence comparable to the normal aged population [225]. A comparison between open and laparoscopic TME showed a similar minimal effect on urinary function but significantly lower sexual dysfunction with laparoscopy [226]. A prospective study, however, did not find any difference between open and laparoscopic resection of rectal cancer; for both groups, sexual dysfunction particularly in men increased immediately after surgery and slightly improved by 12 months, on the other hand, the urinary function was less affected and returned to baseline at 6 months [227]. Another prospective study confirmed that the impact of laparoscopic TME on genitourinary function was a temporary deterioration that was reversed at 1-year follow-up [228]. Technical points leading to the dysfunction could be traced back with the video recording of the surgery. The identification of autonomic nerves using electrical stimulation during laparoscopic proctectomy resulted in a better urinary and erectile function [229].

As expected, surgery for more advanced rectal cancer and adjuvant treatments are associated with higher genitourinary complications. Preoperative chemoradiotherapy for locally advanced rectal cancer was associated with urinary incontinence in one fourth of patients and most men developed ED [230].

56.3.4 Diabetes

The clinical spectrum of DM includes urologic complications involving voiding and sexual dysfunction the underlying pathophysiologic mechanisms are complex affecting nerves, endothelium, and smooth muscle [231]. There is an indirect evidence associating all three pathologies of diabetic neuropathy affecting the lower urinary tract, LUTS, and sexual dysfunction. We assumed that the presence of diabetic cystopathy, OAB, peripheral neuropathy, autonomic neuropathy or diabetic foot is an indicator of neurogenic lower urinary tract dysfunction. Variable associations of these pathologies were reported.

Diabetic cystopathy was found in 43–87% of insulin dependent diabetics and 25% of patients on oral hypoglycemic treatment [232]. Peripheral neuropathy correlated with cystopathy in 75–100% of patients.

Autonomic neuropathy in patients with diabetes was associated with high residual urine and erectile dysfunction [233] and in another study, was diagnosed in 43% of diabetic patients who suffer from ED [234]. Cardiovascular autonomic neuropathy is an independent risk factor that correlated with bladder dysfunction, erectile dysfunction, and peripheral neuropathy [235]. Patients with type 1 DM and cardiovascular autonomic neuropathy had 2.7 greater odds of having sexual dysfunction and LUTS [236]. Both LUTS and ED coexisted in 15% of patients with diabetes mellitus; cardiovascular autonomic neuropathy was diagnosed in 62% of those patients [236].

Diabetic foot and sexual dysfunction were associated in one study. Asian American men who had diabetic foot complained of ED in 52% while 72% of women complained of incontinence [237].

OAB in diabetic men, particularly of the wet type, is significantly associated with severe ED after adjusting for age and duration of DM [238]. The presence of severe ED was a risk factor for urgency incontinence once a week or more. In a study of 502 men with OAB matched with controls, urinary symptoms significantly impacted sexual function [239]. OAB symptoms were significantly associated with decreased sexual activity, decreased enjoyment with sex, decreased sexual satisfaction and more prevalent ED [239].

Long term follow-up of type 1 diabetic patients showed that poor glycemic control is associated with poor quality of life and with several complications including neuropathy, erectile dysfunction, and urinary incontinence [240]. In men with type 1 DM, the quality of life was negatively affected by the presence of ED, LUTS or both [241]. Neuropathy was an independent risk factor associated with poor quality of life, LUTS, and ED. In women, the quality of life was negatively affected by the presence of FSD, UI/LUTS, all of which were independently associated with neuropathy. In men with type 2 DM, the presence of metabolic syndrome did not modify the association between LUTS and ED [242].

56.3.5 Parkinson's Disease

In a large registry of Parkinson's disease (PD), the prevalence of urinary incontinence was 22% in women and 21% in men [243]. Sexual dysfunction affected 8% of women and 30% of men. Age and disease duration were independent risk factors for urinary incontinence, whereas age alone correlated with sexual dysfunction [243]. In a study of patients with PD, compared to controls, there was a significant

increase in the prevalence of irritative (16–63%) and obstructive symptoms (28–70%) and a significant decrease in libido (83–84%), sexual intercourse (55–88%), orgasm (87%), and in men decrease in erection and ejaculation (79%) [244]. The association of ED and bladder dysfunction in patients with PD is significant compared to controls [245]. Motor dysfunction particularly finger taps is associated OAB [246]. Non-motor symptoms, however, including urinary and sexual dysfunction were most prevalent in men with young and late onset PD [247].

56.3.6 Overactive Bladder

Several studies reported an association between OAB and sexual dysfunction in both men and women. In a cross-sectional study in a representative large population-based sample in the UK, Sweden, and the USA, OAB was significantly associated with diminished sexual activity and enjoyment of sex in men and women [248]. Another study evaluated the prevalence of OAB in a large group of men and women [249]. Of the individuals who reported OAB, 17.6% reported a negative impact on sexual life in comparison to 4.7% in those without OAB. The negative impact on sexual life was higher in OAB (wet) affecting 25% versus OAB (dry) affecting 14.4%.

56.3.6.1 Men

In a large population-based sample, OAB was significantly associated with ED and ejaculatory dysfunction but not premature ejaculation [248]. A cross-sectional epidemiologic study showed that urgency with fear of leaking was independently associated with loss of sexual enjoyment, ED, and ejaculatory dysfunction [250].

It is difficult to dissociate LUTS in men due to prostatic enlargement from that due to a neurogenic cause. However, few studies implied that LUTS not due to prostatic enlargement might be associated with sexual dysfunction. In a group of men with LUTS, sexual function, prostate volume, PSA, residual urine, age, and BMI were assessed [251]. Multivariate analysis showed that moderate to severe ED correlated with increasing age and the presence of OAB symptoms, particularly urge incontinence, suggesting that OAB, not related to large prostatic volume or high residual, was associated with ED. Another study indicated that storage symptoms were independent risk factors for ED as seen in motorcyclists with a higher risk of developing LUTS and ED [252].

Several studies were reported on the use of PDE5i in the treatment of LUTS due to prostatic enlargement but only a few evaluated the impact on OAB alone with mixing results. In older men with OAB, treatment with tadalafil 5 mg daily dose was compared to fesoterodine. Both treatments improved the OAB scores with a significant advantage to tadalafil. In addition, tadalafil significantly improved the quality of life and sexual function [253]. In contrast, a multicenter trial to evaluate the efficacy of the PDE5i, UK-369,003 on OAB, reported that patients did not show clinical improvement versus placebo [254]. Only the subset of patients who had associated ED reported better sexual function scores and quality of life. When the etiology of LUTS in men is clearly neurogenic, treatment positively impacted both urinary and sexual function. In men with neurogenic bladder symptoms, sacral neuromodulation improved LUTS and erectile function in patients, particularly with retention [255].

56.3.6.2 Women

Sexually active women reported an association between LUTS and sexual dysfunction. In a large sample of sexually active Turkish women, 52.5% had FSD and 14.6% had urinary incontinence (68% urge or mixed) [256]. Another prevalence study involving sexually active hospital female employees reported that urge incontinence was associated with low vaginal lubrication and sexual pain [257]. Women presenting with urinary incontinence of various types or LUTS were diagnosed with sexual dysfunction in 46% [258]. Several domains of the FSFI were significantly worse than that of controls including desire, lubrication, satisfaction and sexual pain. Risk factors identified in patients with sexual dysfunction were stress incontinence, urge incontinence, recurrent bacterial cystitis, and menopause. Of women with orgasm dysfunction, 46% reported bothersome urge incontinence [258]. Only urge incontinence showed significant association with the domains of sexual pain and lubrication in a recent study among sexually active women with stress, urge and mixed incontinence [259]. There was a mild global association between different types of incontinence and FSD [259].

OAB negatively impacted FSD scores [260]. Sexual activity was less frequent in the wet group. Of the wet group, 50% were sexually active whereas 91% in the dry group were sexually active. OAB negatively impacted sexual desire and ability to reach orgasm in both groups. Anxiety, fear of incontinence during intercourse and pain all contributed to the inability to reach orgasm. A different study reported that as much as one-third of sexually active women with the complaint of urinary incontinence and urgency leaked urine during sexual activity which significantly spoiled their sexual life [261]. On a different note, a study of 40 women with OAB, compared to age-matched controls, the desire was the only FSD parameter that was significantly impaired [262]. There was no difference between the wet and dry groups in FSD.

Menopause is a significant risk factor for both urinary and sexual dysfunction. In a sample of postmenopausal women

who reported incontinence, 69%, 33% had urge incontinence, and 30.5% had mixed incontinence. Of the sexually active women, 84% reported a decline in sexual desire and frequency of intercourse, while 78% experienced a decrease in sexual satisfaction and difficulty in having an orgasm, and 45% dyspareunia [263]. Although 25% of women with OAB had FSD, the significant risk factors were not the bothersomeness from urinary symptoms, rather the menopause and partner status [264].

Urodynamic findings in women with LUTS were correlated with FSD questionnaire; FSD was significantly associated with bladder pain syndrome followed by clinical and urodynamic urgency and urge incontinence [265]. Among women with LUTS, urinary incontinence and detrusor overactivity were associated with the worst FSD scores compared to women with normal urodynamic studies [266]. Clinically, dry OAB had the least negative impact on FSD, whereas mixed urinary incontinence had the worst effect. Women with incontinence at orgasm had 70% detrusor overactivity on urodynamic testing and a modest response to antimuscarinics leaving 41% still symptomatic [267]. Detrusor instability is not only associated with FSD but also with a negative psychological impact [268].

Women referred for evaluation of FSD had an associated urinary incontinence in 36% of cases [269]. These patients demonstrated lower clitoral and vaginal wall sensation compared to patients with only FSD, implicating an underlying sensory nerve pathology. A unique FSD condition was reported and was associated with both urinary symptoms and neuropathy. The restless genital syndrome is a condition where women have persistent genital arousal without sexual desire [270]. It is commonly associated with restless leg syndrome, urinary urgency, urethral hypersensitivity, sensory neuropathy affecting the pudendal and dorsal clitoral nerves and pelvic varices.

Treatment of OAB may have a positive impact on FSD. In a study of women with OAB, treatment with tolterodine significantly improved all domains of the sexual function questionnaire including desire, arousal, lubrication, orgasm, and satisfaction [271]. Postmenopausal women with OAB and FSD were randomized for treatment with antimuscarinic alone (fesoterodine) or combined with estrogen topical vaginal cream [272]. After 12 weeks of treatment, both groups had a significant improvement in the scores of the bladder and sexual function. In an Italian study, 51% of women with dry OAB had FSD [273]. Treatment of those women with percutaneous tibial nerve stimulation resulted in a significant improvement in all domains of their sexual function domains. Interestingly, this improvement was independent of the results of treatment of OAB.

Women with treatment refractory OAB and non-obstructive urinary retention showed an improvement of both urinary and sexual function after sacral neuromodulation [274]. Other studies confirmed this observation. Sacral neuromodulation for neurogenic LUTS resulted in improvement of sexual function in 4/11 women and for idiopathic LUTS in 2/8 [275]. A second study showed that sacral neuromodulation for OAB resulted in a 29% improvement in female sexual function scores at a median follow-up of 3 years [276]. The improvement in sexual function correlated with the clinical improvement of urinary symptoms. On the other hand, a different study showed no significant improvement of FSD with neuromodulation [277].

56.3.7 Other Diseases

Multiple system atrophy (MSA) was reported in association with urinary dysfunction and sexual dysfunction more commonly than in PD and could have provided a clue towards early diagnosis [278]. MSA and LUTS were associated with ED in men [279] and decreased genital sensation in 47% of women [280]. MSA associated genitourinary dysfunction occurred early in the course of the disease, affected all patients by 2 years and was not related to motor symptoms, unlike PD. Progression of MSA correlated with the development of urinary dysfunction but there was no clear correlation with ED progression [281].

Several reports of other neurologic disease showed an association between sexual and urinary dysfunction. Chronic myelopathy due to infection with the human T-lymphotropic virus type 1 (HTLV-1) was commonly associated with ED, urinary symptoms, and OAB [282, 283]. Men infected with HTLV-1 were assessed for the prevalence of ED and OAB. Fifty-five percent of patients had ED which strongly correlated with the presence of OAB [283]. All patients with HTLV-1-associated myelopathy or tropical spastic paraparesis had ED. Patients with a history of transverse myelitis and persistent urinary symptoms showed abnormalities on urodynamic testing and half the men had ED or ejaculatory dysfunction [284]. Neurological Behcet's syndrome was associated with 63% ED and 50% detrusor instability [285]. Patients with Huntington disease had significantly more prevalent autonomic dysfunction including urinary symptoms and in men, ED and ejaculatory dysfunction compared to controls [286]. Autonomic dysfunction correlated with depression. Patients with Charcot-Marie-Tooth neuropathy were compared to healthy controls. Both men and women had significantly worse LUTS scores but sexual function was not affected [287]. And finally, autosomal recessive spastic ataxia of Charlevoix-Saguenay was associated with ED and LUTS [288].

56.4 Shortcomings of the Review

56.4.1 Assumptions

While reporting of sexual dysfunction or urinary dysfunction is readily identifiable in the literature, the identification of the underlying neurological disease is much more subtle. To identify the three pathologies together we had to make a certain assumption that might have omitted some citations and included others that are not necessarily "neurogenic" in etiology. We considered that all citations including urgency, urge incontinence, and OAB as having a neurogenic origin. Although we excluded obvious mechanical obstructive pathology like prostatic enlargement in men and prolapse in women, yet we might have overestimated the neurogenic element because of inclusions of OAB due to a myogenic pathology. A second assumption was that all SCI patients had urinary dysfunction. We did not require in the search syntax that citations on SCI have a urinary dysfunction related term. This might have resulted in the inclusion of some studies on SCI that did not have urinary dysfunction, though uncommon. A third assumption was that diabetic neuropathy was associated with neurogenic bladder dysfunction. Indirect evidence leading to this conclusion included peripheral neuropathy, autonomic neuropathy, and diabetic foot. Therefore, our search might have included some patients who had documented neuropathies but did not affect the urinary bladder. A fourth assumption we made was that patients with benign prostatic hyperplasia or stress incontinence had no underlying neurogenic pathology and we excluded their citations.

56.4.2 Inclusions and Exclusions

We excluded the conditions of painful bladder syndrome, interstitial cystitis, and chronic nonbacterial prostatitis though pain may have been related to a sensory neurogenic cause. Another shortcoming is that we included retrospective publications and those with no objective assessment of sexual dysfunction or urinary dysfunction. Our results are missing reports on the association of DM and retrograde ejaculation as the association with urinary dysfunction was not reported in the studies reviewed. Similarly, no study of dementia or Alzheimer's disease was included as the association of these conditions combined with urinary dysfunction and sexual dysfunction were not identified in our search. Some of the older studies were not included. These were studies on semen quality and ART in SCI patients as a plethora of more recent studies addressed these subjects. Some of the older studies were excluded because they did not provide sufficient information on either LUTS or sexual dysfunction. We did not include certain older citations on sildenafil and penile prosthesis in SCI because many newer publications reiterated similar findings. We omitted reports on some treatments for ED with topical vasoactive medications, and other unique procedures for which efficacy was not supported by subsequent studies.

56.5 Research Suggestions

Studies on sexual dysfunction and SCI need to include more specific data on the nature of urinary dysfunction associated and how it contributes to the condition. More studies involving patients with MS need to address the association of urinary and sexual dysfunction together and assess the correlation between different facets of these conditions. There is a need to objectively identify autonomic neuropathy leading to urinary dysfunction in association with pathologies such as DM, OAB and outflow obstruction. Only then a direct association with sexual dysfunction can be concluded. Reports on fertility and ART are mostly retrospective and include a mixed array of patients, sperm retrieval methods and ART. The choice of ART was frequently selected based on the quality of sperm. In this context, prospective studies and standardized methodology and outcome measures are needed. Finally, although there are multiple reports on the effect of PDE5i on ED of neurogenic origin, and on LUTS associated with benign prostatic enlargement, little is known about the effect of this treatment on neurogenic lower urinary tract dysfunction and none on women LUTS.

56.6 Conclusion

There are many citations in Medline which describe the association of neurogenic pathology and LUTS and likewise the association of neurogenic pathology and sexual dysfunction. The literature, however, is poor in reporting on the association of LUTS of a neurogenic origin and sexual dysfunction. Our search has identified several reports that strongly associate neurogenic LUTS with sexual dysfunction in both sexes. In men ED and ejaculatory dysfunction and in women decreased vaginal lubrication and orgasmic dysfunction was associated with neurogenic LUTS. The most significant urinary condition that correlated with sexual dysfunction was OAB. Although neurogenic LUTS was commonly reported in association with sexual dysfunction, yet women tended to adapt more readily than men. However, men with neurogenic LUTS and ED adapted better than men with ED of other causes. Many reports documented the poor quality of semen of men with SCI and management for couples to treat infertility. However, there is a paucity of data on

infertility in women with neurogenic bladder, its management, and outcomes. Our review has identified many areas that need further research more clearly associating neurogenic pathology, LUTS and sexual dysfunction in patients with SCI, DM, and OAB.

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57 Other Uncommon Complications in Neurogenic Bladder Patients When Neuro-Urology Is Not Part of the Health Care System

Emmanuel J. Braschi

This chapter is describing other uncommon complications in neurogenic bladder patients when neurourology is not part of the health care system.

57.1 Megalithiasis

A 25 years old female patient with a history of myelomeningocele (MMC), who had a bladder augmentation at 7 years of age. The reason of consultation was: recurrent urinary tract infections. The patient was performing bladder intermittent selfcatheterization but during history talking a bad technique and lack of fulfillment of the scheduled catheterizations was detected. It was her first consultation with a neurourologist. Ultrasound performed in her village: renal: "normal" and uninformed bladder: "without repletion." It should be noted that many times studies are performed in their small localities of origin of the patients, and often, the quality of them is not the best. We performed a cystourethrography and vesicoureteral reflux (VUR) was ruled out but three bladder lithiasis were diagnosed, one of them was approximately 10 cm in size. X-ray was performed (Fig. 57.1a). The diagnosis was confirmed by cystoscopy. Open cystolithotomy was performed: three lithiasis were extracted, the largest one was 10.5 cm and another two were 4.5 and 4 cm (Fig. 57.1b). We decided to fragment the stone, so it was not necessary to increase the bladder incision. There was no availability of technology to avoid open surgery. The patient did not return to consultation despite attempts to contact her. She came for the second consultation 5 years later. Second open cystolithotomy was performed: two lithiasis of 63 and 49 mm were extracted. Despite explaining the risks of not respecting the medical indications, the patient failed to continue follow-up. She returned 1 year later and a third cystolithotomy was performed: one lithiasis of 2.5 cm in size was extracted.

- Physico-chemical study of lithiasis: ammonium-magnesium phosphate and to a lesser extent calcium carbonate
- Uroculture: + Enterococcus sensitive to: ampicillin and nitrofurantoin
- Cultivation lithiasis: + Enterococcus
- In evaluation by nephrology, she was diagnosed hypocitraturia: 199 mg/24 h (RV 300–900 mg), which was the reason why started treatment with potassium citrate. She was also diagnosed idiopathic hypercalciuria, which would have hereditary origin, since she had normocalcemia and unexplained hypercalciuria.
- 24 h calciuria: 250 mg/24 h (RV: 60–200 mg/24 h)
- Calcemia: 9.7 mg/dL (RV 8.5–10.5)
- Urine citrate: 199 mg/24 h (RV 300–900 mg)
- Creatinine: 0.86 mg/dL
- Urine citrate: 511 mg/24 h, under treatment with potassium citrate, in spite of that, lithiasis of 2.5 cm.

Patient with great difficulty to comply with the indications and perform a correct follow-up. As previously mentioned, we detected a poor technique of bladder catheterization and little respect for catheterization schedules. Finally, the patient was able to comply with the indications and follow-up guidelines, and as a result she is now stone free at 19 months of follow-up.

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_57

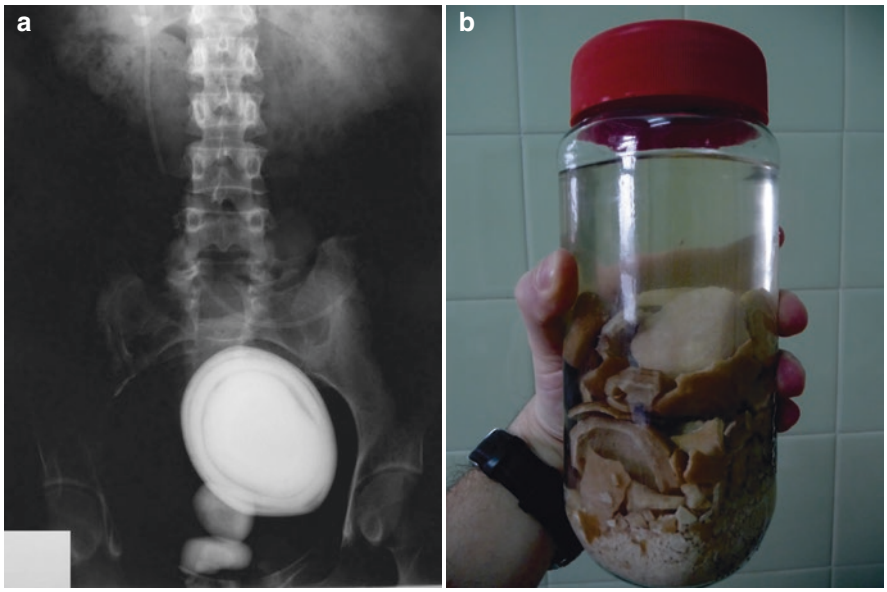

Fig. 57.1 (**a**) Megalithiasis: X-ray was performed and three bladder lithiasis were diagnosed, one of them was approximately 10 cm in size. Myelomeningocele patient. (**b**) Megalithiasis: Open cystolithotomy was performed. Three lithiasis were extracted, the largest one was 10.5 cm and another two were 4.5 and 4 cm

57.2 Multiple Lithiasis

A 18 years old male patient with a myelomeningocele history.

Urinary incontinence consultation associated with recurrent urinary tract infections. The patient reported intermittent bladder catheterization as emptying bladder method. During the interrogation, the findings of the first case were repeated, a poor catheterization technique and lack of respect for the scheduled hours were evident.

An ultrasound study was performed, which reports: 56 mm lithiasis in right kidney and left kidney with moderate hydronephrosis, multiple bladder lithiasis. X-ray of urinary tree was requested (Fig. 57.2).

The diagnosis was confirmed by tomography evidencing right kidney staghorn calculi of 58 mm, moderate hydronephrosis in the left kidney and at least 15 lithiasis in the bladder.

Radiorrenogram with furosemide: Right kidney functional nullification, Left kidney: arrival phase decreased, cumulating parenchymal phase, cumulative excretory phase, no excretion at 20 min, good response to diuretics at 24 h, dilated and tortuous ureters.

Open cystolithotomy was performed obtaining more than 20 lithiasis, being the largest of 5 cm.

- Creatinine clearence: 32.58 mL/min (RV 80–140 mL/min)
- Creatinine: 0.68 mg/dL
- Urine creatinine: 0.34 g/24 h (RV men 0.80–2.00 g/24 h)
- Uroculture: + Proteus mirabilis
- Lithiasis culture: + Proteus mirabilis

When nephrectomy was proposed, the patient's family refused to this surgery. Despite explaining patient's situation, risks and possible consequences, there was loss of follow-up.

57.3 Injury for Misuse of Condom Catheter

A 61 years old male patient with a history of complete (ASIA A) spinal cord injury T12 due to a fall in height from a ladder during his work 4 years ago. To void his bladder, he used to alternate between condom catheter and indwelling catheter. He suffered an injury due to misuse of the condom catheter by adjusting it to prevent it from losing its position (Fig. 57.3). He did not accept intermittent catheterization, and finally he chose a cystostomy.

57.4 Pressure Ulcer

A 45 years old male patient with a history of myelomeningocele. As in all cases, we show the patient's state at the moment of admission to our institution.

Presented a complicated perineum–gluteus–sacral pressure ulcer with chronic osteomyelitis (Fig. 57.4). Chronic use of diapers.

No urethral involvement and a normal kidney-bladder-testis ultrasound. Scrotum with chronic inflammatory changes.

Consequences of poor management of his health care, especially urinary incontinence on the patient's skin could be seen.

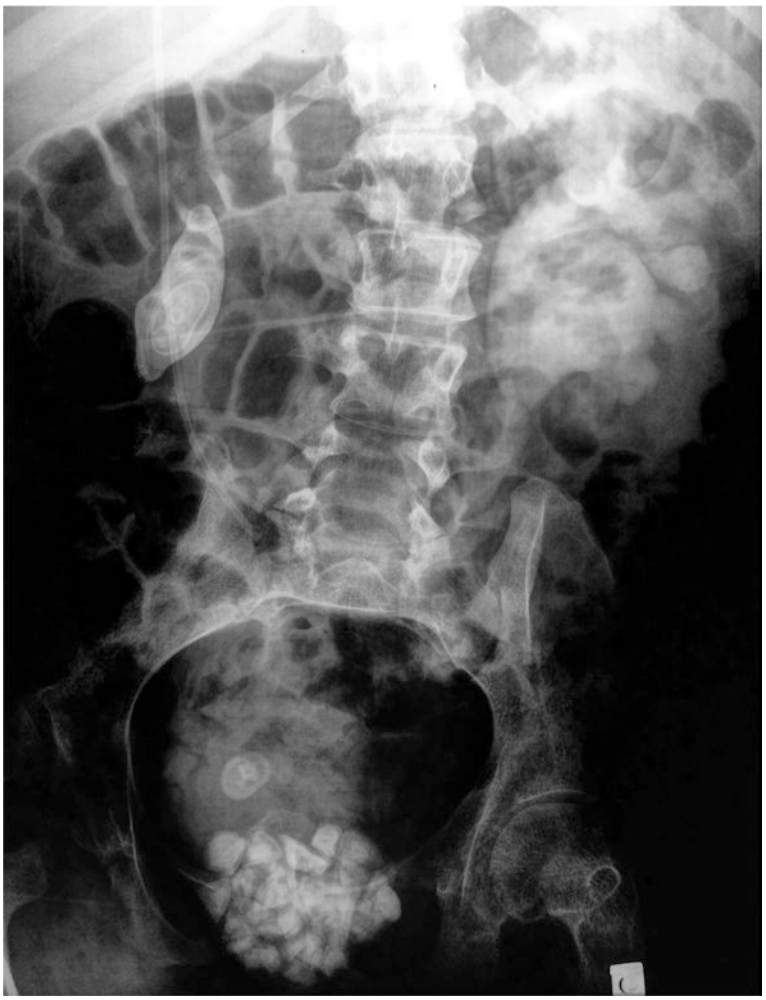

Fig. 57.2 Multiple lithiasis in a myelomeningocele patient. X-ray was performed, which reports: staghorn calculi in right kidney and left kidney with moderate hydronephrosis, multiple bladder lithiasis

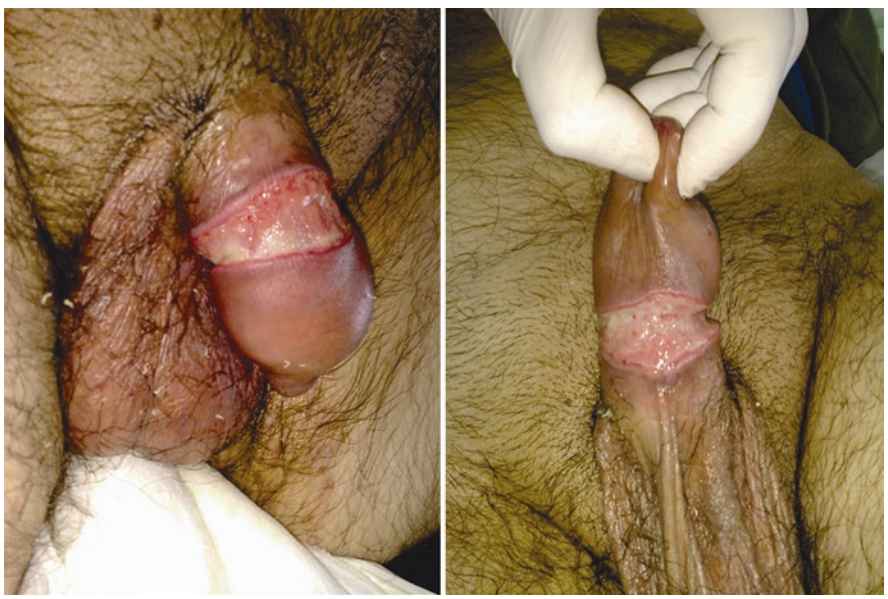

Fig. 57.3 Penis injury due to misuse of the condom catheter by adjusting it to prevent it from losing it's position in a spinal cord injury patient

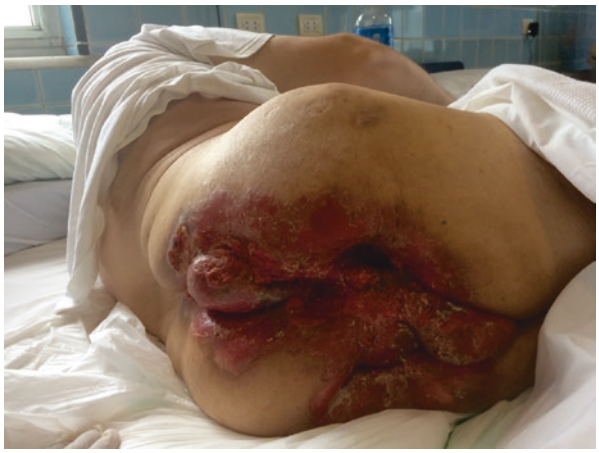

Fig. 57.4 Pressure ulcer. Myelomeningocele patient with complicated perineum–gluteus–sacral pressure ulcer with chronic osteomyelitis

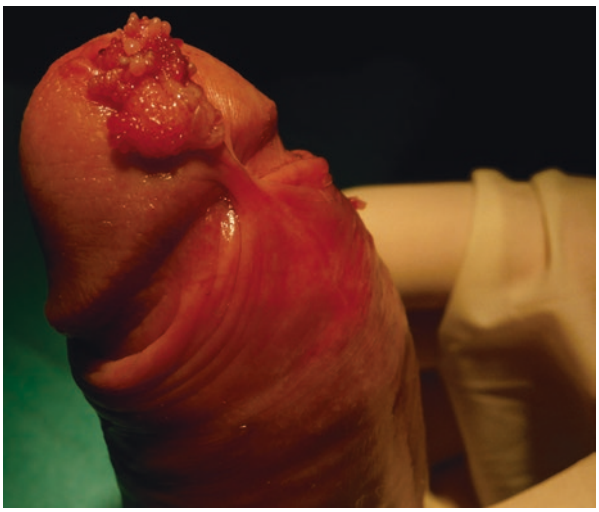

Fig. 57.5 Urethral condyloma. Exophytic polypoid lesion of 2 cm with origin in navicular fossa in a spinal cord injury patient

57.5 Urethral Condyloma

A 24 years old male patient, who had a complete (ASIA A) T6–T7 spinal cord injury, due to a traffic accident riding his motorcycle 3 years ago. History of drug abuse and alcoholism.

The patient reported that voiding through the Credee Maneuver.

Physical examination presented exophytic polypoid lesion of 2 cm with origin in navicular fossa (Fig. 57.5). A cystoscopy was performed which evidences total occupancy of the urethra by condylomas. There was no possibility of video recording.

- Renal and bladder ultrasound reported as unaltered.
- Creatinine: 0.66 mg/dL
- Uroculture: + Providence + Gonococcus
- Endoscopic resection was performed plus percutaneous cystostomy
- The anatomopathological study reported: "condyloma acuminata"

As it used to happen frequently, the patient did not respect the indications nor follow-up guidelines. Returning to consult 1 year after the first resection. On this occasion, he did not only had complete occupancy of the urethra but also had polyps in the bladder. A complete resection of the lesions was performed with the same result in the anatomopathological study.

After the second intervention there was loss of patient's follow-up.

57.6 Uretro–Cutaneous Fistula

A 26 years old patient with a complete (ASIA A) T11–T12 spinal cord injury, 5 years evolution due to fall in height. Antecedents of delinquency and drug abuse.

Use of indwelling catheter from his injury. In his admission evaluation to the institution, there was a typical scrotal—penis angle lesion due to misuse of indwelling catheter (Fig. 57.6a).

Kidney and bladder ultrasound reported as normal.

Surgical intervention was performed jointly with the Plastic and Reconstructive Surgery Service: Urethroplasty plus cutaneous flap by transposition (Fig. 57.6b).

Urodynamic study with perineal surface electromyography after surgery, reported a 580 mL cystometric capacity, maximum detrusor pressure of 46 cm of water, without finding uninhibited contractions, preserved compliance.

The patient was instructed in the technique of intermittent bladder selfcatheterization, which was currently performing without complications (Fig. 57.6c).

57.7 Penis Tumor: Total Penectomy + Cystostomy

A 68 years old male patient with a history of complete (ASIA A) L3–L4 spinal cord injury due to traffic car accident without seat belt 24 years ago with chronic use of diapers. The patient was a countryside worker without medical follow-up of his pathology.

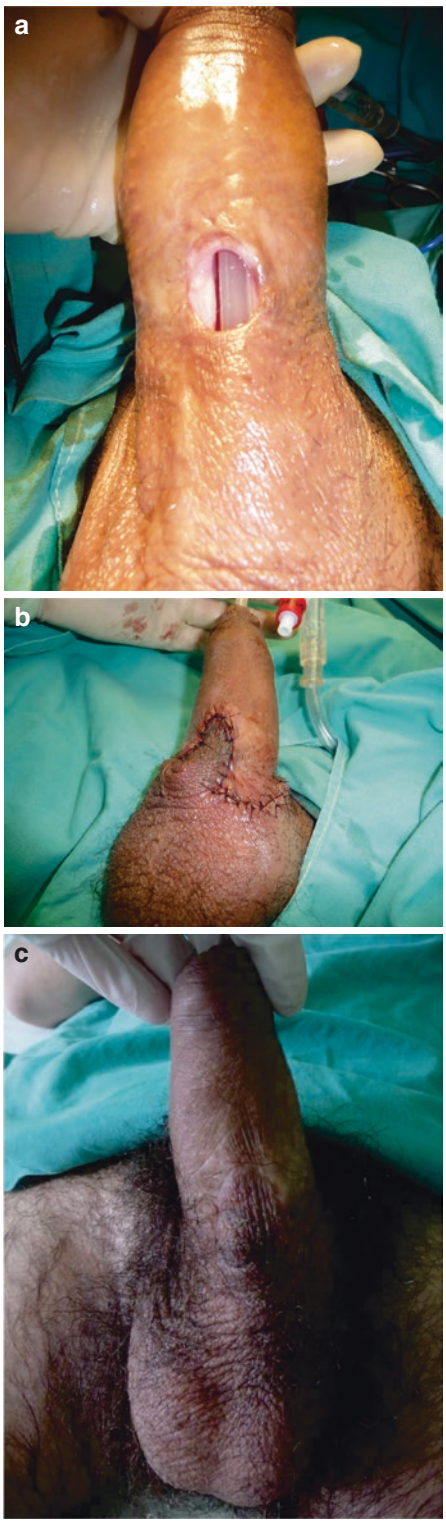

Fig. 57.6 (**a**) Uretro-cutaneous fistula: Typical scrotal-penis angle lesion due to misuse of indwelling catheter in a spinal cord injury patient. (**b**) Uretro-cutaneous fistula: Surgical intervention was performed jointly with the Plastic and Reconstructive Surgery Service: Urethroplasty plus cutaneous flap by transposition. (**c**) Uretro-cutaneous fistula: Postoperative result, 3 months of follow-up

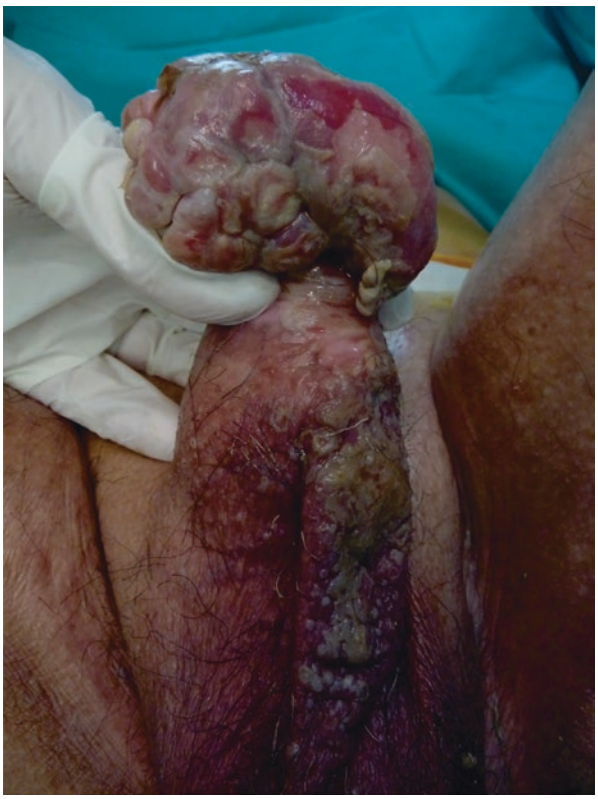

Fig. 57.7 Penis tumor with total penectomy + cystostomy: During the physical examination, an exophytic proliferative mass of 9 cm wide with cauliflower aspect that replaced almost all penile tissue was detected in a spinal cord injury patient

In the Institute Admission Evaluation during the physical examination, an exophytic proliferative mass of 9 cm wide with cauliflower aspect that replaced almost all penile tissue was detected (Fig. 57.7).

Surprisingly, he had a normal renovesical ultrasound.

A total penectomy plus percutaneous cystostomy was performed. Anatomopathological study: "Chronic inflammatory process in activity, abscessed and ulcerated, ruled out malignant neoplastic lesion: Inflammatory Pseudotumor (IPT)." An absolutely rare location for this type of tumor.

The patient had a follow-up of 7 years, with no complications or recurrences.

57.8 Labioplasty Reduction

Hypertrophy of Labia Minora has a high impact on woman's body self-image, a direct impact on her sexual activity and inducing gynecological infections, as well as discomfort for the use of tight clothing or practicing physical activity.

We present the case of an 18 years old patient with a history of myelomeningocele who performed intermittent bladder catheterization and had recurrent UTI.

Neurourological consultation was done because of recurrent urinary tract infections. The kidney and bladder ultrasound was without alterations and a cystourethrography was without vesicoureteral reflux. She was supposed to perform intermittent bladder catheterization but now she presented with a progressive difficulty in recent years to perform self-catheterization. The physical examination showed hypertrophy of the labia minora (Fig. 57.8). She also was aesthetically disconformed.

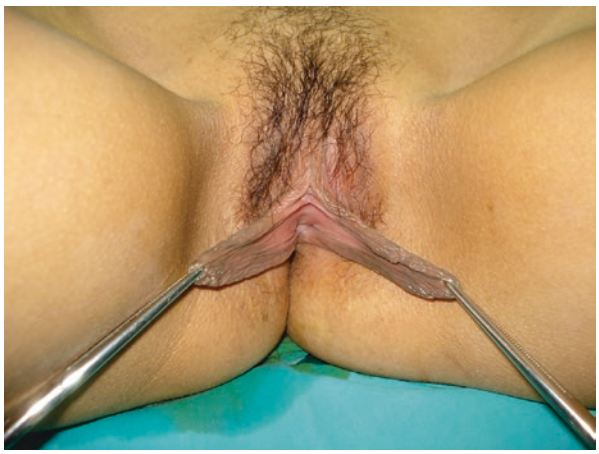

Fig. 57.8 Labia minora hypertrophy in a myelomeningocele patient

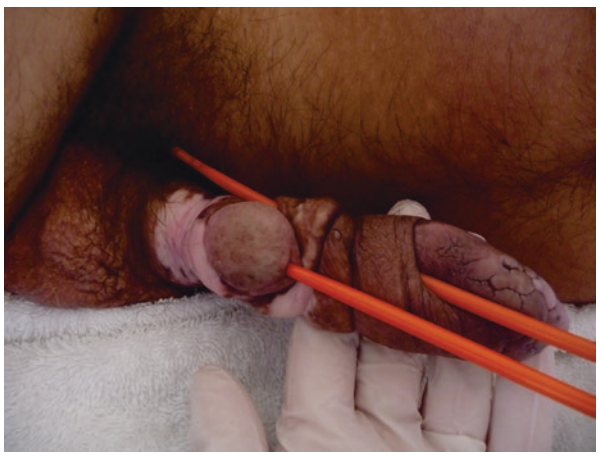

Fig. 57.9 Injury for chronic misuse of condom catheter in a spinal cord injury patient: In the physical examination, a chronic inflammatory prepuce mass was diagnosed, where the glans fistulized through the prepuce

Redundant tissue was excised in a longitudinal manner and the skin was approximated with 3–0 catgut suture. Surgery went well and she was discharged home the same day with an indwelling Foley catheter for 2 weeks. We recommended bed rest for the first 2–3 days and local application of ice to help reduce any local swelling.

At 5 years of follow-up the patient reported a clear improvement in the self-catheterization technique and to be free of urinary tract infections.

57.9 Injury for Chronic Misuse of Condom Catheter

We present the case of a 45 years old male patient with a history of complete (ASIA A) T11 spinal cord injury due to a motorcycle sport accident 18 years ago.

In his first consultation to neurourology, 18 years after his accident, a chronic inflammatory prepuce mass where the glans fistulized through the prepuce was seen (Fig. 57.9).

He presented with normal renal function and renal ultrasound without alterations but with bladder wall hypertrophy.

The patient used a condom catheter from his accident, using a rubber band for fixing. This incorrect technique was suspected as responsible for his chronic injury.

At the moment of proposing a surgical intervention, he refused to perform it.

57.10 Bladder Tumor

A 55 years old female patient with a history of ischemic stroke 5 years ago. Query for episode of hematuria. She reported an increase in urinary urgency and urinary incontinence as well as sporadic episodes of macroscopic hematuria in the last year.

Renal ultrasound without particularities, bladder not informed due to inability of the patient to achieve urinary retention.

An excretory urogram was performed, diagnosing a bladder mass (Fig. 57.10a).

During cystoscopy, a solid-looking bladder mass blocks the bladder neck (Fig. 57.10b).

After completing the staging and biopsy (carcinoma), a radical cystectomy with Bricker was carried out.

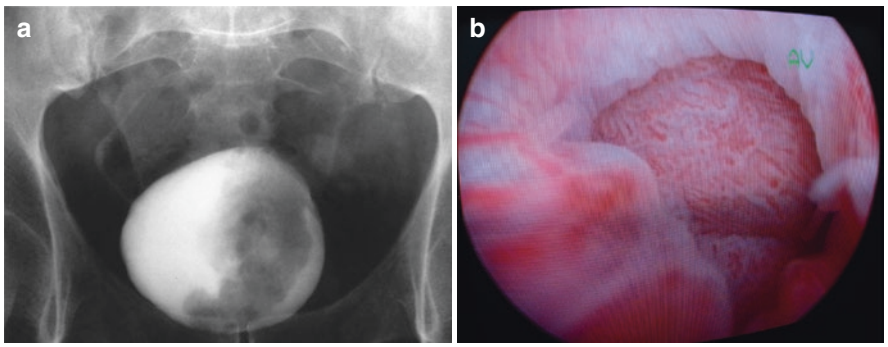

Fig. 57.10 (**a**) Bladder tumor: Excretory urogram showing a bladder mass in a stroke patient. (**b**) Bladder tumor: Cystoscopy showed that a solid-looking bladder mass blocked the bladder neck

Part XVIII

Follow-Up

Follow-Up

58

Peter Zvara

Due to their complex etiology and pathogenesis, symptoms of neurogenic bladder differ significantly in their pattern, severity, degree to which they impact quality of life as well as their potential to lead to complications. Guidelines for diagnostic and therapeutic algorithms exist and are being periodically updated. The need for individualized "risk adapted" management has been stressed in recent years. The main goal of neurogenic bladder therapy is preservation of the upper urinary tract and achievement of complete or at least socially acceptable urinary continence. This is very important as incontinence represents a symptom with a most pronounced effect on the quality of life.

Neurogenic bladder dysfunction is a dynamic condition, which changes over time. It is therefore essential that every patient be regularly evaluated by a urologist. The regular follow-ups allow for the timely adjustment of therapy to coincide with changes in the course of disease and early detection of risk factors, which could lead to complications. Methods used in the follow up, including the frequency of follow-up, have to be individualized. Urological literature published to date contains mostly data assessing the treatment and follow up of patients following spinal cord injury (SCI). Data from randomized clinical studies, which allow for formulating recommendations for daily clinical practice in other neurogenic bladder dysfunctions are sparse.

58.1 Patient Follow-Up Following Spinal Cord Injury (SCI)

The role of a urologist with appropriate expertise is essential in instituting the therapy immediately after injury. Once the bladder function is stabilized, yearly re-evaluations by an experienced urologist, experienced rehabilitation doctor or general practitioner with expertise in paraplegic cases is recommended. The routine follow up visits should include the patient's interim history. Special attention should be paid to the identification of risk factors including febrile urinary tract infections (UTIs), recurrent UTIs (more than two episodes per year) and hypertensive crises (related to autonomous dysreflexia). In addition, we evaluate the method of urinary bladder evacuation, degree of continence, changes in concomitant medication, frequency of bowel evacuation and sexual function. Basic vital functions including heart rate, blood pressure and body temperature must be evaluated and recorded. The local examination looking for skin problems, pressure sores, inspection of external genitalia, and rectal examination is obligatory. A basic neuro-urological examination should include sensitivity in sacral dermatomes, evaluation of anal sphincter tone and sacral reflexes. Every follow up visit should also include a review of the patient's voiding diary.

Urinalysis and a microscopic evaluation of urinary sediment should be performed at every follow up visit as well. More than 50 leucocytes in the urinary sediment under a high-power field, even in an asymptomatic patient, correlates with a higher risk of febrile UTIs [1]. Some argue that the sensitivity of the dipstick method is sufficient for basic screening [2]. Urinalysis and urine culture necessary any time the patient reports symptoms of a UTI. It has been documented that approximately 60% of patients are able to reliably correlate their symptoms with the presence of a UTI. In all remaining cases, however, patients report UTI symptoms even in the absence of leucocyturia and bacteriuria. Therefore, diagnosing a UTI based exclusively on symptoms, without urine culture and sensitivity, could lead to unjustified use of antibiotics [3].

A urine culture at every follow up visit in all (symptomatic and asymptomatic) patients is becoming a routine practice for many urologists. This approach is based on the assumption that SCI patients generally have an increased risk of UTIs caused by resistant bacterial strains. Information

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_58

regarding the type and sensitivity of bacteria identified in previous urine cultures would therefore help in selecting the appropriate therapy, once symptomatic UTI develops. Penders et al., however, documented a high variability of bacterial strains, which colonize the lower urinary tract. They concluded that the results of past urine culture evaluations have no value in predicting the appropriate antibiotic therapy once symptoms develop. These authors recommend performing urine culture in symptomatic patients every time prior to selecting the therapy [4].

Blood analysis should include blood count (hemoglobin, hematocrit, leucocytes, thrombocytes), markers of inflammation (i.e. C-reactive protein—CRP), and renal function testing. Liver tests should be performed in patients who have been on long term and/or high dose anticholinergic therapy. Creatinine, used for evaluation of kidney function in the general population, has a limited utility in SCI patients. Creatinine is a final product of myocyte metabolism. Denervation-induced muscular atrophy following SCI leads to reduced muscle mass decreasing endogenous creatinine production. Furthermore, the serum creatinine levels remain normal until the glomerular filtration decreases by 50% or more. These two phenomena cause creatinine levels in SCI patients to remain within the physiologic range of healthy individuals, even when their renal function is significantly impaired. Therefore, the use of cystatine C is recommended for the renal function assessment. This protein has been shown to correlate with creatinine clearance and it is not dependent on muscle mass, age, or sex [5, 6].

A kidney ultrasound is an essential part of every follow up examination. It is a broadly accepted screening tool with high sensitivity and specificity, especially for detection of additional risk factors such as dilatation of the collecting system, nephrolithiasis and change in bladder morphology (hypertrophy of the bladder wall, pseudodiverticula or cystolithiasis). In the case of inconclusive findings, other diagnostic methods, such as computer tomography (CT), should be used. Additional diagnostic methods are justified based on abnormalities found in the basic evaluation and risk factors associated with complications.

Urodynamic evaluation including videourodynamics is currently the only diagnostic tool that can identify the following risk factors: high pressure conditions (low detrusor compliance, early and/or prolonged detrusor contraction), detrusor overactivity in the voiding phase, increase in trabeculation, significant detrusor-sphincter dyssynergia, ballooning of the posterior urethra, vesico-ureteral reflux and influx into the male adnexa. There are no guidelines regarding the frequency of urodynamic evaluation. It has been suggested that it should be performed in all patients once a year during the first 3–5 years after injury [7]. Subsequently, in patients with stable neurourological findings, is suggested that urodynamics be performed every 2–3 years [8]. Yearly urodynamic evaluations should continue in patients with risk factors of upper urinary tract damage. The most significant risk factors include high intravesical pressure, long-lasting uninhibited bladder contractions and low cystometric capacity. Other risk factors include suprasacral spinal cord lesions, febrile and/or recurrent UTIs (more than two episodes per year), repeated episodes of autonomous dysreflexia, abnormal results on the ultrasound, X-ray or CT of kidneys, ureters and bladder, and persistent abnormal laboratory parameters (high sedimentation rate, high white blood count, and elevated serum levels of CRP or cystatine C) [9–11]. Urodynamic or videourodynamic evaluation should also be performed when a significant change of symptoms, such as newly developed or worsened incontinence, occur or when change in therapy is considered due to lack of efficacy. Urodynamics is especially important prior to any invasive treatment.

The incidence of bladder cancer in patients following SCI is higher than in healthy individuals [12]. The reason for this remains unclear. It has been speculated that it could be a result of chronic inflammation or mechanical irritation due to long lasting catheterization. Microscopic and macroscopic hematuria in patients after SCI is common, due to frequent UTIs, urethral trauma during catheterization and frequently used anti-aggregation therapy. Therefore, the value of the presence of hematuria as well as urine cytology as a cancer screening method in SCI patients is limited. Regular annual cystoscopy remains the only screening method for early detection of bladder tumors. Special attention has to be given to patients with permanent indwelling urethral or suprapubic catheters [13].

Additional diagnostic methods could be used in the long-term follow up of SCI patients. They, however, have to be carefully considered and justified based on the individual case and presence of risk factors.

58.2 Follow-Up for Patients with Spinal Dysraphisms

Inherent defects of the spinal cord cause disruption to the innervation of the lower urinary tract. Based on type and extent of damage, this could lead to a variety of disturbances to the bladder and sphincteric unit. Most patients with spinal dysraphisms suffer from incontinence. It has been reported that, if not properly treated, deterioration in upper urinary tract function occurs in 30–40% of patients [14].

In such a population, comprehensive physical evaluation, laboratory tests, ultrasound and urodynamic evaluation should be performed early after birth. This examination should provide a detailed functional evaluation of the lower urinary tract, assess the synergy between the bladder and its outlet, and identify risk factors. The most significant risk fac-

tors are detrusor-sphincter dyssynergia, high detrusor leak point pressure (>40 cm/H_2O), low bladder compliance (<9 mL/cm/H_2O), acontractile detrusor and dilatation of the collecting system of the kidney. Even in patients with no evidence of the above listed risk factors at initial evaluation, there is a 32% risk of worsening urodynamic findings. In most cases, this is due to development of tethered cord syndrome [15]. Tethered cord syndrome is characterized by the dislocation of the medullar conus, below the second lumbar vertebrae, caused by a fibrous band (filum terminale), which is fixed to the base of the dural sack. This syndrome occurs usually around ages 5–6 and later during puberty, due to the accelerated growth of the vertebral column. Stretching of the spinal cord structures leads to the development of a large variety of skeletal, proctological and urological symptoms. A common symptom is the development of pain in the lumbosacral area. It has been documented that the worsening of urodynamic parameters could be an early symptom of tethered cord syndrome [16]. Early detection of disease progression based in the urodynamically identified pathology could lead to timely surgical release of arachnoid adhesions. This could lead to improvement of symptoms and better overall prognosis. Improvement of the urodynamic findings could serve as evidence of successful surgical intervention [17].

It is therefore recommended to perform a complete urological assessment including urodynamics or videourodynamics in all patients on a yearly basis until completion of rapid growth at the end of puberty. The follow up of adolescents and adults must be individualized based on careful analysis of symptoms, the history of the disease, dynamics of the disease and efficacy of the ongoing treatment. Additionally, age-related changes in self-esteem have to be carefully considered on a case-by-case basis.

58.3 Follow-Up of Patients Suffering from Multiple Sclerosis (MS)

In Europe, MS is the most prevalent immune-mediated neurological disease. LUTS develop in up to 75% of MS patients [18]. Storage symptoms are more common than symptoms associated with bladder evacuation. The most frequent urodynamic abnormality is detrusor hyperactivity [19]. Variability of LUTS over time, following a worsening trend as the disease progresses in the majority of these patients. The prevalence of functional upper urinary tract deterioration is reported to be between 1 and 3% [20]. Patients who are wheelchair or bed bound with an expanded disability symptom score above 6.5 and have severe incontinence, individuals with an indwelling catheter or suprapubic epicystostomy and patients with primary or secondary progressive MS, are at the highest risk [21, 22]. In contrast to SCI and spinal dysraphisms, the main rational for a regular life-long urological follow up in MS patients is the changes in symptoms over time. Sufficient data suggesting a definitive recommendation regarding an optimal follow up schedule are lacking. The urological follow up is based on a clinical assessment, review of the voiding diary, urine analysis, ultrasound, and uroflowmetry with a post void residual (PVR) measurement. The regular PVR measurement is essential in patients with voiding symptoms and those with storage symptoms treated with anticholinergics.

The role of invasive urodynamics is controversial. The arguments supporting regular urodynamic evaluation include:

- Urodynamics is considered the gold standard in the diagnosis of neurogenic dysfunction of the lower urinary tract
- In many cases, symptoms do not correlate with urodynamic findings [23, 24]

More recently, some have supported the treatment and follow up of these patients based on noninvasive diagnostic methods. This opinion is based on the following evidence:

- Low risk of upper urinary tract deterioration
- The treatment of patients with evacuation dysfunction does not differ whether they have weak bladder contraction or functional bladder outlet obstruction
- The first line of treatment for patients with storage symptoms, regardless of presence or absence of detrusor overactivity is antimuscarinics
- Regular comprehensive urodynamic testing is time consuming and requires significant resources (both personal and financial)

The currently prevailing opinion is that performing invasive urodynamics should be reserved for patients with significant risk factors for upper urinary damage, failing the first line of treatment and for those for which invasive therapy is being considered.

Prevention, diagnostics, and treatment of UTIs represent an additional issue in long-term follow up of MS patients. UTIs are considered a significant risk factor for the progression of MS [25]. Increased incidence of urological malignancies in MS patients has also been documented [26]. Special attention with regards to early cancer detection must be given to patients treated with azathioprim [27].

58.4 Follow-Up of Patients with Other Types of Neurogenic Bladder

Data supporting the formulation of a set of guidelines for the long-term follow up of patients with other types of neurogenic bladder dysfunction are lacking. In patients with detrusor

overactivity and preserved coordinated micturition without detrusor-sphincter dyssynergia (i.e. dementia, stroke, suprapontine lesions), non-invasive diagnostic methods (clinical examination including neuro-urological evaluation, voiding diary review, urinalysis, uroflowmetry, postvoid residuum, laboratory tests to address the renal function) are recommended. In patients with voiding dysfunction (i.e. diabetic neuropathy, lower motor neuron lesion), the efficacy of the micturition must be evaluated. In these cases, the main goal of the follow-up is early determination of the time point at which clean intermittent catheterization must be introduced. In stabilized patients, the non-invasive diagnostic methods are recommended.

Patients suffering from Parkinson's disease develop complex lower urinary tract symptoms (LUTS). A comprehensive urodynamic evaluation is required to elucidate the underlining pathophysiology, especially in patients for whom invasive treatment methods are to be considered. Differentiation between functional bladder outlet obstruction due to sphincter spasticity and anatomical obstruction due to benign prostatic hyperplasia represents a significant issue, which could only be addressed with the use of invasive urodynamics [28]. The optimal follow-up should be proposed by a urologist with expertise in this field. It is critical that the clinical situation, risk factors, and response to previous treatment are considered in the treatment plan. The ultimate goal of the long-term follow up is to achieve the best possible quality of life.

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Part XIX

Specificities of Neurogenic Bladder from Some Nervous System Diseases

Cerebrovascular Accidents

59

Bryan J. Hill, Casey G. Kowalik, Joshua A. Cohn, and Roger R. Dmochowski

Abstract

Post stroke urinary incontinence (PSI) is a relatively common occurrence after a stroke, or cerebrovascular accident. The most common pattern of micturition disturbance immediately following a stroke is urinary retention proceeded by resolution or the development of urge urinary incontinence (Lee et al., Neurourol Urodyn 36:136–141, 2017). The majority of patients with PSI demonstrate urodynamic evidence of detrusor overactivity (DO) (Pettersen and Wyller, J Am Geriatr Soc 54:1878–1884, 2006). The diagnosis of the underlying cause of the urinary incontinence may guide clinicians to apply the most efficient management strategies, particularly when conservative therapies have failed (Abrams et al., Neurourol Urodyn 29:213–240, 2010). Compared to patients who are continent after a stroke, the development of urinary incontinence following a stroke is associated with an overall poorer prognosis with increased morbidity and mortality (Patel et al., Stroke 32:122–127, 2001).

59.1 Symptoms

Worldwide, the prevalence of stroke in persons 65 years and older ranges from 4.6 to 7.3%. Strokes are more common in men than women, and the prevalence of stroke increases with age [1]. Strokes are associated with significant morbidity such as cognitive decline, motor decline, and voiding dysfunction. The prevalence of urinary incontinence (UI) after stroke ranges from 28 to 79% [2–4] and the development of urinary incontinence following a stroke is associated with an overall poor prognosis and increased mortality [5].

Immediately following a stroke, the most common urinary symptom is retention. One hypothesis for this finding is related to the concept of cerebral shock in which there is an absence of higher level signaling to initiate micturition in the presence of hypotonic muscles resulting in detrusor under-activity [6]. In a prospective study of patients 72 h after an acute stroke, urinary retention occurred in 47% of patients [7]. However, another prospective study with 2-month follow-up of patients experiencing post-stroke urinary retention found that 96% of patients had resolution of urinary retention [8].

After the initial onset of urinary retention most patients go on to either experience resolution or improvement of retention symptoms with or without subsequent development of urinary incontinence. This is often referred to as post-stroke urinary incontinence (PSI). One prospective study found that one week after a stroke the PSI rate was 55% and declined to 21% at 12 weeks [3]. Another prospective study performed in patients admitted for inpatient management of symptoms following a stroke found an initial rate of UI of 79%, which increased over 30 days to 81% [2]. A study of 39 patients with average follow-up of 19 months after stroke found that urinary urgency and urgency incontinence occurred in 26/29 (67%) patients [9].

Because strokes often occur in older patients, many patients experience baseline urinary incontinence. Therefore, it is helpful to understand the prevalence of urinary incontinence in this population. In a prospective study of 315 patients admitted to a geriatric stroke and rehabilitation unit in a community hospital, 46% had underlying pre-existing micturition dysfunction. Urge urinary incontinence (UUI) was present in 31% of patients and urge predominant mixed urinary incontinence occurred in 9%. In continent patients, 12% experienced other micturition disorders including urgency and frequency

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and voiding difficulty. After a stroke, 25% of patients developed new micturition disturbances. The most common symptom was UUI (83%), followed by retention (12%), and then urgency/frequency without UUI (5%). In the 98 patients with pre-existing urinary incontinence prior to having a stroke, 81% had no change in UI whereas 18% experienced a change from baseline [10]. Another common cause of urinary incontinence in this population may be detrusor hyperactivity with impaired contractility (DHIC) which is characterized by an overactive bladder that does not effectively empty. While usually presenting as urinary incontinence, these patients may also exhibit symptoms of urinary retention [11].

The size of the stroke is strongly associated with PSI. Gelber found that larger infarcts (cortical plus subcortical lesions) were associated with the development of urinary incontinence. In regression analysis, patients with large lesions were 5.3 times more likely to be incontinent than in patients with only cortical or only subcortical strokes. Other factors strongly correlated with urinary incontinence were aphasia and overall poorer functional status, which also contribute to functional incontinence independent of bladder pathophysiology. No association was found between the laterality of stroke lesion and the development of UI. A likely mechanistic explanation for this is the bladder sphincter is bilaterally innervated [2, 12].

59.2 Urodynamic Changes

Complaints of voiding dysfunction are often not predictive of urodynamic findings [13]. There may be different pathophysiological mechanisms for post-stroke urinary incontinence which include detrusor overactivity, cognitive and or language impairment in the setting of normal bladder function, or overflow incontinence related to neuropathy or medication side effects [14]. In addition to a thorough history and physical exam, urodynamics may offer the clinician insight into the underlying pathophysiology of PSI and guide treatment [4].

The most common urodynamic finding after a stroke is detrusor overactivity (DO) with complete bladder emptying [3, 4, 15]. Gelber reported that 21 days after a stroke, 37% of patients experienced DO, another 37% had normal studies, 21% had detrusor under-activity (DU), and 5% had detrusor-sphincter dyssynergia (DSD) [12]. These numbers may be slightly different by gender. In patients with DO, 35% of men had bladder outlet obstruction and 13% of women had inefficient bladder emptying. Urodynamics may be especially valuable in this sub-group of patients in order to avoid unnecessarily worsening of urinary incontinence by prescribing medications that may further reduce voiding efficiency in the setting of a voiding disorder [16].

Urodynamic findings may change as time progresses from the initial urodynamic evaluation after a stroke. A prospective study by Pizzi et al. of patients admitted to a post-stroke rehabilitation unit found that after 30 days the number of normal studies increased from 15 to 30%, DO decreased from 56 to 48%, rates of DU were similar from 15 to 16%, and DO with impaired contractility decreased from 14 to 6%. Factors associated with incontinence were age and functional disability, while gender, stroke laterality, and time from stroke to study entry were not associated with incontinence [2].

Urodynamic findings may vary with the size and type of stroke. A prospective study of 45 men and 15 women reported on urodynamic findings by the location of lesions within the brain 72 h after an acute stroke. Fifty-two percent of patients had DO on cystometrography and a majority of these patients had lesions from the cerebral cortex and internal capsule [7]. These findings were similar to a study by Tsuchida et al. who found DO in 51% of patients, and the most common associated brain lesion was the frontal lobe and internal capsule [9]. When EMG studies were done of the external sphincter in patients with DO who had cortical or internal capsule lesions, the patients were unable to voluntarily contract the external sphincter during DO. An additional finding was that seven of the 33 patients had detrusor under-activity. The most common lesion on CT scan in patients with DO was the cerebral cortex and in patients with DU were a combined lesions of the cerebral cortex and basal ganglia [15]. The type of stroke (ischemic versus hemorrhagic) may also reflect urodynamic changes. Han et al. [17] found DO was more common in patients with ischemic stroke (71%) than with hemorrhagic stroke (35%), while detrusor underactivity (DU) was more common in hemorrhagic stroke (65%) than with ischemic stroke (29%). The authors hypothesized that hemorrhagic strokes may have a more prolonged acute effect on cerebral dysfunction due to delayed resolution of cytotoxic edema and hydrocephalus compared to ischemic strokes.

59.3 Diagnosis

A thorough history and physical exam is necessary to determine if there are findings warranting urodynamic evaluation. A helpful mnemonic to use in assessing for potentially modifiable causes of urinary incontinence is DIaPPERS: delirium, infection, pharmaceuticals, psychological, excess urine output, reduced mobility, and stool impaction [18].

The clinician should determine if there was urinary incontinence prior to the stroke. Additional information should include: the onset of urinary symptoms after a stroke, the type of urinary symptoms (frequency, urgency, and difficulty voiding), the progression of symptoms (worsening or improving), and the use of collection mechanisms (diapers, indwelling catheters, pads, self-catheterization). Prior professional incontinence evaluations should be reviewed [4]. The patient's functional capacity should be evaluated. This includes an assessment of activities of daily living (ADLS) and instrumental activities of daily living (IADLs). The use

Table 58.1 Methods of assessing functional capacity in patients after stroke

ADLS	Eating, bathing, dressing, toileting, walking, transferring
IADLS	Managing finances, managing medications, navigating transportation, shopping, preparing meals, performing housework, using the telephone, performing basic home maintenance
Modified Rankin[a]	
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight diability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinence, and requiring constant nursing care and attention
6	Dead

ADLS activities of daily living, *IADLS* instrumental activities of daily living

[a]Van Swieten JC, Koudstaa PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604

of impairment scales is helpful. A commonly used impairment scale is the modified Rankin shown in Table 58.1 [19]. Additional scales include the Barthel index of activities of daily living and the Frenchay activities index [4].

Physical exam should include a thorough vaginal or genitourinary exam. A 3-day bladder diary tracking of fluid intake and urine output as well as symptoms experiences may be helpful. Urodynamics should be considered when there is an inadequate response to initial medical therapy or the patient is experiencing difficulties with bladder emptying [4]. Knowing the underlying cause for the urinary incontinence may help improve management strategies.

Recent joint recommendations from the American Urological Association and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) recommends performing urodynamics for patients with neurogenic bladder or relevant neurological conditions defined as "those neurogenic disorders of the [lower urinary tract] LUT dysfunction that may predispose a patient to upper tract complication(s)." They recommend the following: Post void residual (PVR) assessment either in the initial visit or during urodynamic assessment, complex cystometrogram (CMG), pressure flow studies (PFS), fluoroscopy at the time of urodynamics (VUDS) if available, and electromyography (EMG) in combination with CMG with or without pressure-flow studies [20].

There is insufficient evidence for the use of urodynamics to determine the stroke type, location, or extent of the stroke. Urodynamic studies are most useful to help determine the underlying cause of PSI and to help guide the clinician in medical and or surgical management [4].

59.4 Treatment

The general approach is to rule out reversible causes of urinary incontinence first, then proceed with conservative management, followed by medical management and then specialized management. In a recent Cochrane review on the management of PSI, the authors state that "specialized professional input using systematic methods to assess and manage continence problems may improve some outcomes." This is especially important in the time period immediately following a stroke as it may have a positive impact during the management of long-term sequelae of the stroke [21].

Conservative options include timed voiding every 2–3 h, fluid restriction (if excessive intake is occurring), and pelvic floor muscle training [4]. In a prospective study of 19 incontinent post stroke patients, 13 were treated with scheduled voiding and 6 pharmacologically. The patients that were treated with scheduled voiding had fewer incontinence episodes than those who were treated pharmacologically [12]. In patients who are severely debilitated, urinary collection appliances (catheters, pads, diapers) are initial options but may not be feasible long term and may lead to unnecessary infections and skin breakdown from irritation from urine. Often urinary and bowel function are both impaired and must be managed together [4, 22].

Medication therapy should focus on the use of medications with the least deleterious cognitive side effects. Oxybutynin, especially at higher doses, may impair cognitive function in elderly persons, while solifenacin and trospium may result in less cognitive impairment [4, 23]. Mirabegron, a selective β3-adrenoceptor agonist, theoretically may be less likely to result in cognitive impairment due to its absence of anticholinergic properties, but there is limited evidence of its efficacy and side effect profile in the elderly post-stroke population [23].

Specialized treatment for PSI can be guided from the diagnostic findings on urodynamics. For patients with PSI due to DO, initial options include: behavioral modification (timed voiding, fluid restriction), intermittent catheterization with anti-incontinence medication, timed voiding, external urinary collection (pads, diapers) with anti-incontinence medication, or indwelling catheter with anti-incontinence medication. Patients who fail these treatments may need third line treated options such as neuromodulation or intradetrusor botulinum toxin injections. End stage surgical options include enterocystoplasty or urinary diversion [22].

For patients with PSI caused by DO with DSD, intermittent or indwelling catheterization with an anti-incontinence medication is the initial option for conservative treatment. For patients who fail, options include sacral neuromodulation, transurethral incision of the sphincter, enterocystoplasty, or urinary diversion [22].

In patients with incontinence associated DU, conservative options include the following: intermittent or indwelling

catheterization or bladder expression (via Valsalva or Credé maneuver) in select patients in whom such a strategy results in adequate emptying without transmitting elevated detrusor pressures to the upper tract. In patients who fail conservative specialized management, options include transurethral incision of the sphincter, botulinum toxin to the urethral sphincter [22].

For patients with urinary incontinence due to sphincteric incompetence, initial management is timed voiding and external collection appliances. Surgical management includes artificial sphincter, sling (for women), bulking agents, or bladder neck closure with suprapubic catheter or urinary diversion in severe refractory cases [22].

Much of the management of PSI is derived from review articles, expert opinion, and management strategies from studies in patients with neurogenic bladder [4]. More high-quality studies are needed to address management strategies in the sub-population of patients with post stroke urinary incontinence.

59.5 Prognosis

Patients who experience PSI are more likely to have long term morbidity and increased mortality compared to patients who do not have urinary incontinence after a stroke. In a prospective study following 235 stroke patients over 2 years, PSI declined over time, from the initial (40%), 3-month (19%), 1 year (15%), and 2-year (10%) assessment. Regression analysis showed that compared to continent post-stroke patients, patients with PSI had an overall higher mortality rate, higher institutionalization rate, were more likely to be severely or moderately disabled, and had a higher Rankin disability score. Urinary incontinence after a stroke has been associated with approximately four times (OR 4.43) increased odds of death or disability [5].

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Parkinson's Disease

60

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60.1 Introduction

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra. In addition to the movement disorder, patients with PD often show non-motor disorders. The non-motor problems of PD include neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders [1]. Bladder dysfunction is one of the most common autonomic disorders [2, 3]. Studies have shown that the bladder dysfunction has great significance in relation to quality-of-life measures, early institutionalization, and health economics [4, 5]. It is particularly important to note that, unlike motor disorder, bladder dysfunction is sometimes non-responsive to levodopa, suggesting that they occur through a complex patho-physiology [6]. This is because pathology of PD is not confined to the degeneration of dopaminergic neurons in the substantia nigra, and involves other locations in the brain and other neurotransmitter systems than the dopaminergic system. For this reason, add-on therapy is required to maximize patients' quality of life. We here review bladder function and its management of patients with PD, with an understanding of brain-bladder relationship.

60.2 Brain-Bladder Relationship

60.2.1 The Frontal Cortex-Basal Ganglia Circuit Normally Suppresses Micturition

The lower urinary tract (LUT) consists of two major components, the bladder and urethra. The bladder has abundant muscarinic M2,3 receptors and adrenergic beta 3 receptors [7]. The urethra has abundant adrenergic alpha 1A/D receptors and nicotinic (somatic) receptors (Fig. 60.1). The LUT performs storage and emptying of urine, both of which require an intact neuraxis that involves almost all parts of the nervous system [8]. This is in contrast to postural hypotension, which arises due to lesions below the medullary circulation center in humans [9].

Normal storage is dependent on not only the sacral autonomic reflex [7, 10] but also the brain, particularly the pontine storage center [11, 12]. The pontine storage center lies just ventrolateral to the pontine micturition center (PMC). The storage function is also facilitated by the hypothalamus, cerebellum, basal ganglia, and frontal cortex, as shown by functional neuroimaging in humans [13]. Normal micturition is dependent on the spino-bulbo-spinal autonomic reflex, which particularly involves the midbrain periaqueductal gray matter (PAG) [14–17] and the PMC [7, 11]. The PAG is thought to be the switch center from storage to voiding. The PMC is located in or adjacent to the locus coeruleus [18–20]. The PMC projects spinal descending fibers (containing glutamate) to the sacral bladder preganglionic nucleus [21]. PMC also projects fibers (containing gamma-amino-butyric acid (GABA) and glycine) to the sacral urethral motor nucleus (the Onuf's nucleus) [22]. The switch mechanism in the PAG is thought to be regulated by the higher brain structures, e.g., the hypothalamus and prefrontal cortex, some of which overlaps the storage-facilitating area [13, 23]. Bladder (detrusor) overactivity (DO) is the major cause of urinary urgency/frequency and incontinence. In lesions above the brainstem, the micturition reflex arc is intact, where DO is considered an exaggerated micturition reflex [24–26]. The exaggeration of the micturition reflex might also be brought about by facilitation of glutamatergic and D2 dopaminergic pathways [27].

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_60

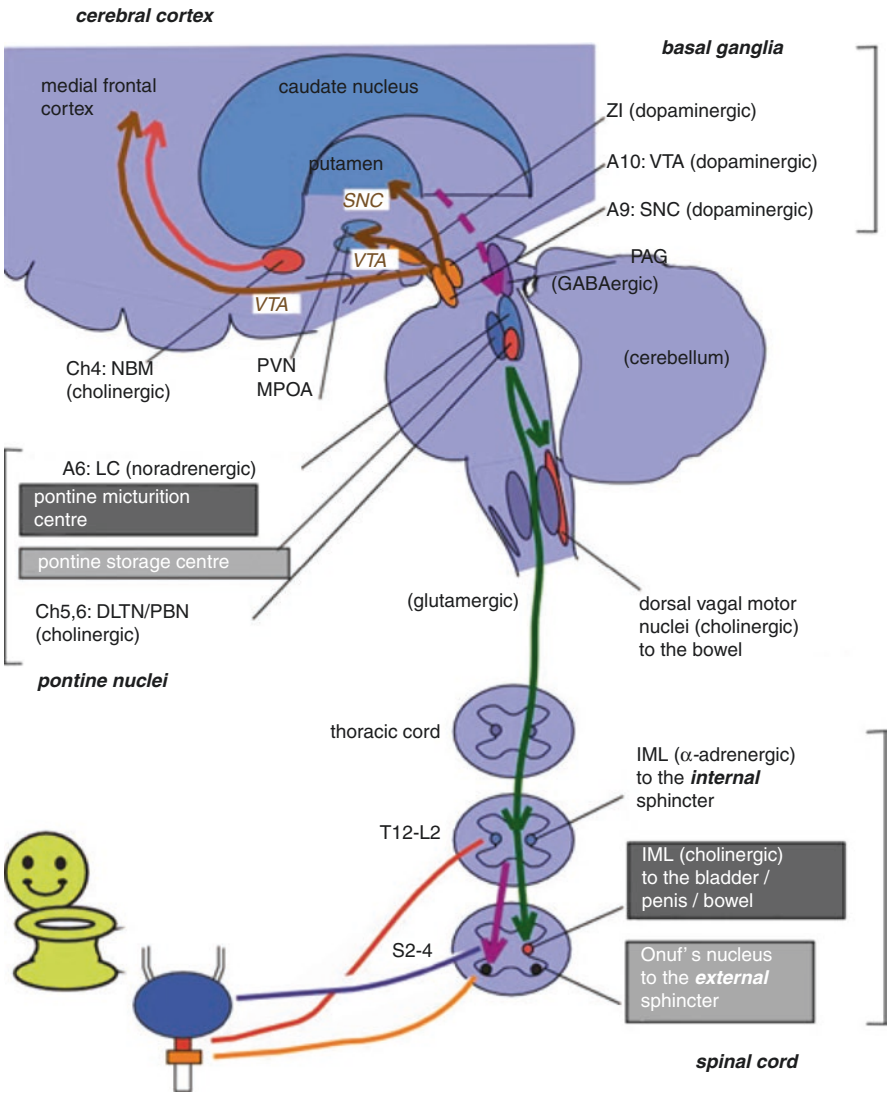

Fig. 60.1 Neural circuitry relevant to micturition. *PAG* periaqueductal gray, *LC* locus ceruleus, *NBM* nucleus basalis Meynert, *PVN* paraventricular nucleus, *MPOA* medial preoptic area, *A* adrenergic/noradrenergic, *ZI* zona incerta, *VTA* ventral tegmental area, *SNC* substantia nigra pars compacta, *DLTN* dorsolateral tegmental nucleus, *PBN* parabrachial nucleus, *IML* intermediolateral cell column, *GABA* gamma-aminobutyric acid, *T* thoracic, *L* lumbar, *S* sacral. See text

60.2.2 Altered Frontal Cortex-Basal Ganglia Circuit Leads to Detrusor Overactivity in PD

The net effect of the basal ganglia on micturition is thought to be inhibitory (Fig. 60.2) [7, 28–30]. Functional neuroimaging during bladder filling results in activation in the globus pallidus of normal volunteers [31] and in the putamen in patients with PD [32]. In contrast, dopamine transporter imaging was lower in PD patients with urinary dysfunction than in those without it [33, 34]. Electrical stimulation of the substantia nigra pars compacta (SNc) inhibited the micturition reflex [35, 36], and striatal dopamine levels *in situ* significantly increased in the urinary storage phase in experimental animals [37]. The micturition reflex is under the influences of dopamine (both inhibitory in D1 and facilitatory in D2) and GABA (inhibitory) [7, 28]. Both the SNc neuronal firing and the released striatal dopamine seem to activate the dopamine D1-GABAergic *direct pathway* (Fig. 60.2), which not only inhibits the basal ganglia output nuclei, but also may inhibit the micturition reflex via GABAergic collateral to the micturition circuit [37–40], particularly to the PAG [41]. In patients with PD, disruption of this pathway may lead to DO and resultant urinary urgency/frequency. In addition to the nigrostriatal fibers, the ventral tegmental area (VTA)-mesolimbic dopaminergic fibers are thought to be involved in the control of micturition [36, 42, 43] (Fig. 60.1).

The frontal cortex has been regarded as the higher center for micturition [44] because lesions in the frontal cortex produce detrusor overactivity in humans [8, 45, 46]. Functional neuroimaging in normal volunteers using positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) is able to show brain activation in response to

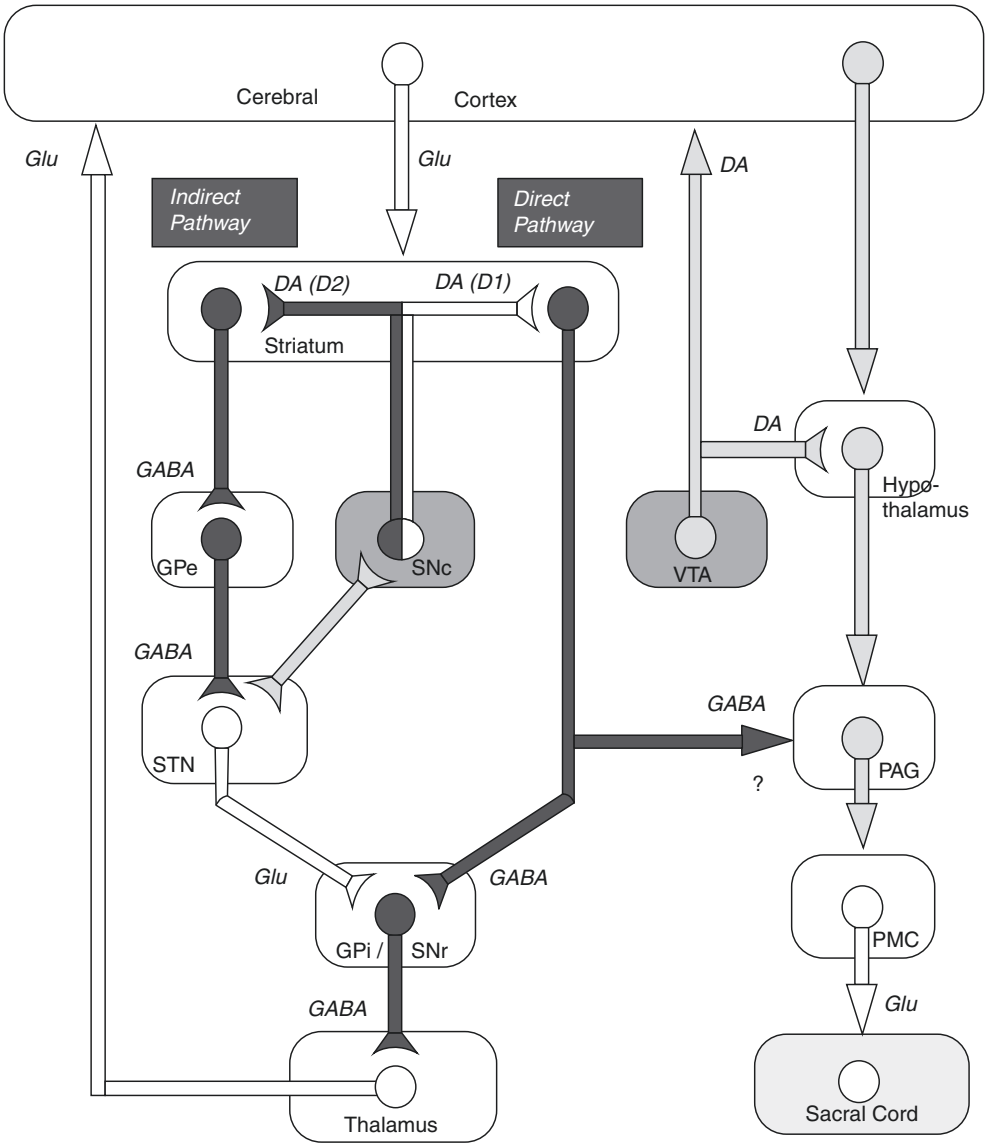

Fig. 60.2 Possible relationship between basal ganglia circuit (left-side) and micturition circuit (right-side). Modified from Sakakibara et al. 2003 [39]. *DA* dopamine, *GABA* gamma-aminobutyric acid, *SNc* substantia nigra pars compacta, *GPi* globus pallidus internus, *SNr* substantia nigra pars reticulate, *STN* subthalamic nucleus, *GPe* globus pallidus externus, *VTA* ventral tegmental area, *PMC* pontine micturition centre, *Glu* glutamate, black line inhibitory neurons, white line excitatory neurons, hatched line neurons of undetermined property. The micturition reflex (right-side pathway) is under the influences of dopamine (DA) (both inhibitory in D1 and facilitatory in D2) and gamma-aminobutyric acid (GABA) (inhibitory). The substantia nigra pars compacta (SNc) neuronal firing and the released striatal dopamine seem to activate the dopamine D1-GABAergic *direct pathway*, which not only inhibits the basal ganglia output nuclei (e.g., the globus pallidus internus [GPi], substantia nigra pars reticulata [SNr]), but also may inhibit the micturition reflex via GABAergic collateral to the micturition circuit. High frequency stimulation (leading to inhibition) in the subthalamic nucleus (STN) also results in bladder inhibition. See text

bladder fullness and urination [8, 47]; and the activated areas strikingly overlap the lesions described in clinical studies. Women with urge urinary incontinence show frontal deactivation as compared with control [48]. The frontal cortex has direct fiber connections with the hypothalamus and the PAG; whereas it might regulate micturition via the basal ganglia circuit as indicated by experimental studies [49] and by fMRI studies [50, 51].

60.3 Bladder Function of Patients with PD

60.3.1 Lower Urinary Tract Symptoms (LUTS) Estimates Up to 65% in Patients with PD

The reported prevalence of LUT symptoms (LUTS) in patients with PD ranges from 38 to 71% [52–57]. However,

it has been difficult to determine to what extent PD contributes to LUTS. Men older than 60 years of age may have bladder outlet obstruction due to prostate hyperplasia. Women may have stress urinary incontinence. "Idiopathic DO" [10] may occur in men and women older than 65 years due in part to latent brain ischemia [58]. Some of the studies were published before the diagnosis of multiple system atrophy (MSA) [59] was recognized. In recent studies of PD patients who were diagnosed according to modern criteria [5, 60–62], the prevalence of LUTS was found to be 27–63.9% using validated questionnaires [60–62], or 53% in men and 63% in women using a nonvalidated questionnaire that includes a urinary incontinence category [5], with all of these values being significantly higher than the incidence rates in healthy controls. The majority of patients had onset of bladder dysfunction after appearance of motor disorder. Correlations have been shown between bladder dysfunction in patients with PD and neurological disability [60], and bladder dysfunction and stage of disease [5], both suggesting a relationship between dopaminergic degeneration and LUTS. However, Campos-Sousa and colleagues did not find such a correlation [62].

60.3.2 Overactive Bladder Is the Major Symptoms in PD

LUTS are divided majorly into two; storage symptoms and voiding symptoms. Storage symptoms are the most common of the LUTS symptom types in PD. Storage symptoms include nocturia (nighttime urinary frequency), which is the most prevalent symptom reported by patients with PD (>60%) [5, 60–62]. Patients also complain of urinary urgency (33–54%) and daytime frequency (16–36%). Urinary incontinence was present in 26% of male and 28% of female patients with PD [5].

60.3.3 Though Post-Void Residual Is Minimum, Some PD Patients Complain Difficult Voiding

Although less common than storage symptoms, voiding symptoms also occur in PD patients. In the study by Sakakibara and colleagues, PD patients had significantly higher rates of retardation in initiating urination (44% of men only), prolongation/poor stream (70% of men only), and straining (28% of women only) compared with the control group [5]. Araki and colleagues noted a correlation between voiding symptoms and stage of disease [63]. However, despite the voiding symptoms, PD patients have low post-void residuals [5].

60.3.4 Urodynamically, Detrusor Overactivity and Mild Weakness Are Common in PD

The storage-phase urodynamic abnormalities in PD include reduced bladder capacity together with detrusor overactivity (DO) in 45–93% [64–69] of patients, which is well correlated with the questionnaire [69], and uninhibited external sphincter relaxation in 33% [53] of patients. Therefore, DO can be the major contributing factor to overactive bladder in PD. There is also a correlation between DO and stage of disease [64].

Pressure-flow analysis of the voiding phase in PD has shown weak detrusor activity during voiding (40% of men; 66% of women) [65]. There is a correlation between a weak detrusor and the stage of the disease [64]. A subset of PD patients had DO during storage but weak detrusor activity in voiding. This combination has recently been estimated to occur in 18% of patients with PD [70]. Some older studies described detrusor-external sphincter dyssynergia or pseudodyssynergia in PD, and these findings were attributed to PD by analogy with bradykinesia of the limbs. However, in our patients with PD, detrusor-external sphincter dyssynergia was rare [65]. In contrast, a pressure-flow analysis in PD revealed that half of the patients with PD showed mild urethral obstruction [65]. Patients with PD are reported to have high resting urethral pressure [71], probably as a result of medication—i.e., levodopa and its metabolites, such as norepinephrine [71]. Irrespective of voiding symptoms in PD, the average volume of post-void residuals in PD was as small as 18 mL [65].

60.3.5 Bladder Function Can Differentiate PD from Multiple System Atrophy (MSA)

In the differential diagnosis of PD and parkinsonian type MSA, large post-void residuals, open bladder neck, and neurogenic change in sphincter motor unit potentials are all common in MSA [65, 72], whereas they are rarely seen in clinically typical PD [73]. However, recent evidence suggests that PD with dementia, or dementia with Lewy bodies [74], may have large post-void residuals and neurogenic change in the sphincter motor unit potentials [75], thereby mimicking MSA.

60.3.6 Transurethral Resection of the Prostate Is Not Avoided in PD

Several studies indicated that most men with PD undergoing transurethral prostate resection for benign prostate hyperplasia (TUR-P) were successful in up to 70% and remained continent 1 year after surgery [76], although TUR-P may lead to

urinary incontinence due to detrusor overactivity. Thus, PD should no longer be considered a contraindication for TUR-P provided that preoperative investigations including urodynamic assessment indicate typical bladder outlet obstruction [77]. This is in clear contrast to MSA that inevitably leads to urinary retention; therefore in MSA, TUR-P should be avoided except for particular indication.

60.3.7 Bladder Function in PD Correlates with Other Clinical Features

It is reported that bladder dysfunction in PD parallels other autonomic dysfunctions [78], cardiac denervation by MIBG scintigraphy [79], and fall [80].

60.4 Treatment of Bladder Dysfunction in PD

60.4.1 Various Effects of Dopaminergic Drugs: Improvement or Worsening

It is possible that levodopa and other antiparkinson medication may affect bladder function in PD. Aranda and colleagues [81] studied the effects of 3–8 mg apomorphine injection on the storage function in two *de novo* PD patients, and found that the bladder capacity increased. They gave oral levodopa to one of the patients, and the bladder capacity increased. We compared the frequency of bladder dysfunction in *de novo* PD and PD with levodopa. In that study, LUTS was less frequent than in the treated group [68]. In another study, after 3 months of treatment with levodopa, the storage urodynamic parameters were slightly improved in *de novo* PD [82].

In contrast, in treated patients, studies concerning the effect of dopaminergic drugs on micturition have produced conflicting results. Regarding overactive bladder, some reports have shown a storage-facilitating effect of dopaminergic drugs [5]. In contrast, Kuno and colleagues showed that a change in medication from bromocriptine (D2 selective agonist) to pergolide (D1 < 2 agonist) brought lessening of nocturia [83], and Yamamoto described improvement of DO by pergolide [84]. Benson and colleagues [85] gave 2000 mg of levodopa in two longstanding PD patients, and bladder capacity increased in both patients. After discontinuation of levodopa, the bladder capacity further increased in one of the patients, but decreased in the other. Other reports have shown a voiding-facilitating effect of dopaminergic drugs [86]. Fitzmaurice and colleagues [67] have described that, in advanced PD with the on-off phenomenon, DO worsened with levodopa in some patients and lessened in others. Winge and colleagues [87] found that the effect on micturition of treatment with dopaminergic drugs in PD was unpredictable. Recent studies have shown that in early PD, a single dose of levodopa exacerbates DO in the filling phase [88]. In contrast, in advanced PD with the on-off phenomenon, a single dose of levodopa either exacerbated [6] or ameliorated bladder storage function [89]. Effect on voiding function was converse in that study, e.g., voiding efficiency was improved [6]. Bromocryptine, a D2 selective agonist, also exacerbated storage function in PD [90]. We still do not know the exact reasons for the discrepancy.

There are several factors underlying the complex bladder behavior in treated PD patients [91]. Post-synaptic dopamine D1 (excitatory) and D2 (inhibitory) receptors have a millimolar affinity to dopamine, whereas dendritic D2 (inhibitory) autoreceptors have a picomolar affinity to dopamine [92]. Therefore, levodopa may first stimulate dendritic D2 autoreceptors, which might suppress the dopaminergic cells and facilitate the micturition reflex. In cases of PD under long-term treatment with levodopa, dopamine receptors are downregulated and potential hypersensitivity might occur [93]. The A11 dopaminergic cell group lies in the dorsal-posterior hypothalamus, which is affected in marmosets with MPTP-induced parkinsonism [94]. This cell group descends as the sole source of spinal dopamine [95], which might also involve in generating bladder overactivity [96]. Peripheral dopamine D1 and D2 receptors also exist in the bladder [97], although their exact role has not been delineated. In addition, in experimental animals, single dose of apomorphine exacerbated the rats' bladder at a high dose, then ameliorated the bladder at a low dose (biphasic effect) [98].

60.4.2 The First Line: Cholinergic Drugs with Care for Cognitive Function

Anticholinergics (muscarinic acetylcholine [ACh] receptor antagonists) [99] are generally used as a first-line treatment for overactive bladder (OAB). However, it is important to balance the therapeutic benefits of these drugs with their potential adverse effects. When the dose of drug increases, post-void residuals may appear. Dry mouth and constipation are common [100].

Cognitive adverse events by anticholinergics are a concern particularly in the elderly. Previous data suggested that a centrally acting anticholinergic, trihexyphenidyl (for ameliorating PD), exacerbated cognitive function in experimental animals and humans. The same was reported for atropine (before endoscopy/surgery) and scopolamine (hyoscine) (for colicky pain or motion sickness). Although oxybutynin has been developed as a peripherally acting drug, recent research suggests that it has some adverse effects on cognitive function in PD with bladder function [101]. Factors underlying the cognitive effects of these medications include: (1) central

muscarinic receptor affinity, e.g., high M1-receptor selectivity; and (2) easy penetration of the blood-brain barrier (BBB), e.g., high lipid solubility (water versus oil partition coefficient [LogP] < 3; number of hydrogen bonds < 8); a neutral charge or low degree of ionization (polar surface area < 90 A); and a less bulky (number of rotatable bonds < 5) and smaller molecular size (<450 Da) [102, 103]. Regarding central muscarinic receptor affinity, most anticholinergics are non-selective muscarinic blockers. The exception is darifenacin, which is an M3-selective antagonist (under manufacture). Regarding BBB penetration, most anticholinergics have a molecular size between 300 Da and 400 Da. However, among these, oxybutynin can readily penetrate the CNS, since it has high lipophilicity and neutrality. Other anticholinergics have less marked lipophilicity or neutrality. Trospium, a quaternary amine, has a particularly high polarity.

In elderly patients who have both overactive bladder and dementia (PD with dementia/dementia with Lewy bodies) [75], treatment of dementia and bladder is a matter of controversy. However, it is known that once cholinergic drugs (donepezil, rivastigmine, etc.) penetrate the BBB, cholinergic agents within the brain is thought to ameliorate bladder storage function [104, 105]. Although with extreme caution, patients with both overactive bladder and dementia could to be manageable, with a combination of centrally-acting cholinergic agent and peripherally-acting anti-cholinergic agent [106, 107]. This treatment needs close observation of patients with an assistance of caregivers.

Only recently, mirabegron, a selective beta-3 adrenergic receptor agonist, became available in the treatment of OAB [108, 109]. Mirabegron acts on beta-3 adrenergic receptors, which indirectly relate with M2 cholinergic receptors but no cognitive adverse events are reported so far. Phosphodiesterase (PDE) 5 inhibitors are originally developed to treat male erectile dysfunction, by inhibiting degradation of neuronal/non-neuronal nitric oxide (a potent smooth muscle dilator) in the cavernous vessels. PDE5 inhibitors are reported to be useful in the treatment of female sexual dysfunction as well as OAB [108, 110]. These drugs are expected as effective drugs for OAB in patients with PD in future.

The pedunculopontine nucleus sends a cholinergic input to dopaminergic neurons in the substantia nigra pars compacta (SNc) and the subthalamic nucleus, playing a significant role in setting and/or modulating the firing pattern of the nigrostriatal neurons [111]. Nicotinic receptors are thought to have augmenting action, whereas M2/4 muscarinic receptors are thought to have inhibitory action [112, 113]. Historically, in late 1800s hyoscyamine, a classical anticholinergic, has been prescribed for PD patients by Charcot. Charcot of Piti Salpetriere Hospital in Paris rediscovered and named this disease 'Parkinson's disease' according to James Parkinson in London. Since then, PD-anticholinergics (trihexyphenidyl, etc.) are widely used for ameliorating motor disorder, particularly for intractable rest tremor. In contrast, PD-anticholinergics may cause drug-induced parkinsonism/dyskinesia in experimental animals [114] and humans [115], presumably depending on occupancy of brain ACh receptor subtypes. Similarly, OAB-anticholinergics may, though extremely-rarely, cause drug-induced parkinsonism in experimental animals [116] and humans [116, 117]. Also, PD-anticholinergics are being contra-indicated in elderly patients because of potential cognitive decline [118].

60.4.3 The Second Line: Serotonergic, Desmopressin, and Others

When a first-line treatment fails or is contraindicated, a second-line treatment might be considered. Bladder training is reported to be effective in PD with urinary incontinence [119].

The main action of central 5-hydroxytryptamine (5-HT, or serotonin)-ergic neurons on the LUT is facilitation of urine storage [120]. In PD, neuronal cell loss in the raphe nucleus has been documented [121]. Therefore, serotonergic drugs, such as duloxetine and milnaciplan [122] can be a choice to treat overactive bladder in PD. Nocturnal polyuria should be distinguished from overactive bladder. In patients with PD, the imbalance between diurnal and nocturnal production of urine can be observed in the course of the disease [123]. Treatment with desmopressin proved to be effective in reducing nocturia in PD [124], although this medication needs extreme caution of water intoxication.

60.4.4 Newer Modalities: Deep Brain Stimulation Improves Bladder in PD; Botulinum Toxin Is Promising in Difficult Cases

The subthalamic nucleus (STN) is regarded as the key area in the basal ganglia *indirect* pathway, which is dominant in the parkinsonian state. Deep brain stimulation (DBS) in the STN inhibits many cells within the STN, probably due to depolarization block and release of GABA from activation of inhibitory afferent terminals (Fig. 60.3) [125]. In the STN, neuronal firings related to the micturition cycle have been observed in cats [39] DBS in the STN proved to have an inhibitory effects on the micturition reflex in animals [39, 40] and in patients with PD [50, 51, 126–128]. DBS in the STN also increased bladder capacity and facilitated

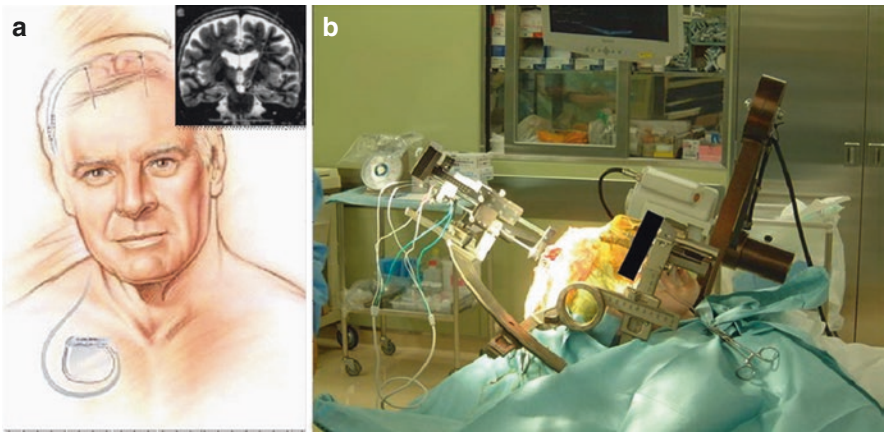

Fig. 60.3 Deep brain stimulation. (**a**) Scheme of the subthalamic nucleus (STN) stimulation by an implanted pulse generator. A cartoon indicates pulse generator-leads connection, not the exact location of STN. Right upper figure indicates the exact location of leads into the STN. (**b**) Leads insertion into the target nucleus (STN) (courtesy from Professor Nagao in Neurosurgery, Sakura Medical Center, Toho University)

bladder afferent pathways in the brain of PD patients [50, 51]. In contrast, when DBS lessens the bladder so much, it may lead to urinary retention [129]. There are some trials that percutaneous posterior tibial nerve stimulation [130] or transcranial magnetic stimulation [131] might ameliorate overactive bladder in patients with PD.

Finally, intramural, multiple botulinum toxin injection in the bladder seems to be a promising method to treat intractable detrusor overactivity in patients with PD [132, 133].

60.4.5 A Guideline for the Management of Bladder Dysfunction in Parkinson's Disease and Other Gait Disorders

We would like to introduce briefly a recently-published guideline for the management of bladder dysfunction in PD. This guideline is made by the Neurourology Promotion Committee in The International Continence Society (ICS).

PD patients commonly have an OAB. We use the following flow chart when seeing this type of patient (Fig. 60.4a): First, even though most bladder disorders in PD patients may be caused by PD itself, we check for common bladder diseases. Among these, male PD patients over 50 years of age are checked for benign prostatic enlargement by cystoscopy and ultrasound sonography. Outlet obstruction can be determined with pressure-flow urodynamics. Similarly, female PD patients over 50 years of age are checked for stress-induced urinary incontinence (UI), e.g., UI during physical stress, through a detailed analysis of patient history. Further detection of pelvic floor decent can be made using chain urethrocystography or stress urodynamics. PD patients over 50 years of age are checked for polyuria. A bladder diary can reveal polyuria (urine output > 3000 mL a day) or nocturnal polyuria (urine output night-time > 33% of a day). Neurologists may start the patient on antiparkinsonian drugs for motor symptoms. Second, the effect of antiparkinsonian drugs on OAB (drugs might be given by neurologists for motor function) is assessed. If the OAB is ameliorated, then the antiparkinsonian drugs benefited the bladder. However, the drug may not significantly change bladder conditions. Third, if necessary the patient is started on anticholinergic drugs for lessening OAB. If the OAB is ameliorated, then we follow up with the bladder. We also care for cognitive adverse events by asking caregivers and patients, or performing a cognitive screening test because anticholinergics may worsen cognitive function, particularly in elderly patients. Notably, post-void residuals (PVR, by ultrasound sonography or catheterisation) may increase (more than 100 mL) if the OAB treatment does not produce significant effects. If the PVR increases, the anticholinergic medication can be titrated or changed. In this case, we try to ascertain the urologic and neurologic causes of urinary retention, which can include MSA.

Clearly, it is not the responsibility of urologists to make a differential diagnosis for neurological diseases. However, urologists should have a brief bedside strategy for the differential diagnosis of such patients, because it is not uncommon that patients visit urologists first. Elderly gait disorder/easy fall is often accompanied by LUTS. The exact reason for this is not clear. However, it is possible that both bladder and gait disorders originate presumably from the same brain lesions involving the prefrontal/mediofrontal area and basal ganglia neural circuit. Gait disorders in elderly individuals are mainly parkinsonian, e.g., slow, short-stepped gait without laterality. Bladder disorders in elderly individuals consist mainly of OAB. Figure 60.4b illustrates how we can manage elderly individuals with gait & bladder problems.

60.5 Conclusions

This article reviewed the current concepts of bladder dysfunction in PD. Central nervous system pathology is clearly associated with bladder dysfunction (urinary urgency/fre-

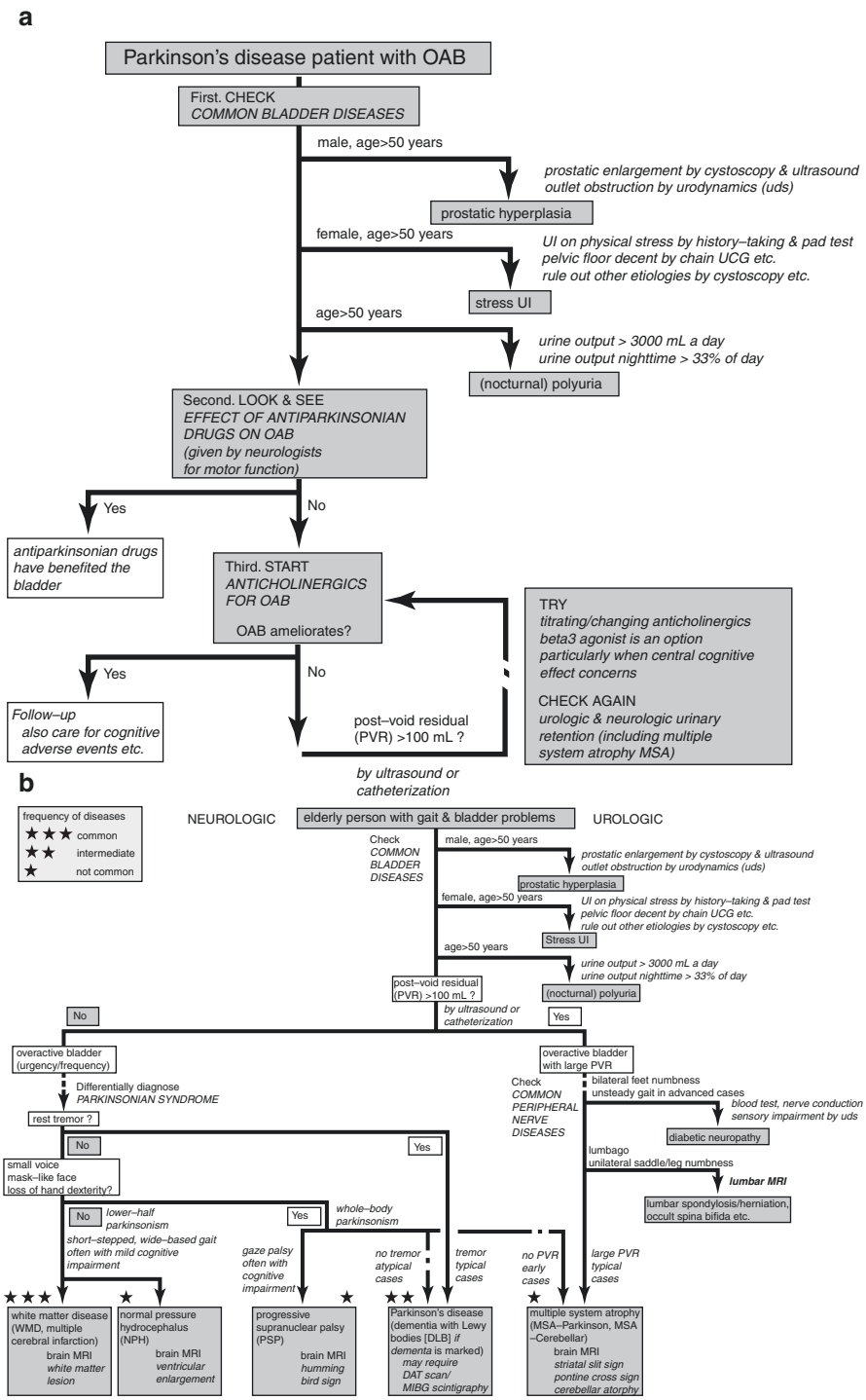

Fig. 60.4 (**a**) A flow chart for bladder management of Parkinson's disease patients with an overactive bladder (previously diagnosed cases). See text. Cited from: A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders [134]. (**b**) A flow chart of differential diagnoses for PD, MSA, and other parkinsonian disorders with LUTS (undiagnosed cases). See text. Cited from: A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders [134]

quency) in PD. Anticholinergic agents and possibly beta-3 adrenergic receptor agonist are the choice to treat bladder dysfunction that do not easily penetrate the BBB. These treatments are beneficial in maximizing patients' quality of life. The ICS guideline is a good reference for urologists to manage such patients.

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Dementia

61

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61.1 Introduction

Dementia is a pathological, neurodegenerative process leading to progressive decline in cognitive and functional abilities. It has multiple causes, diverse manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes [1] (Table 61.1).

The dementias can be classified into four major groups, (1) Alzheimer's disease; (2) vascular dementia (post stroke dementia); (3) the Parkinson's group (including Lewy Body disease, dementia of Parkinson's and Alzheimer's dementia with Parkinson's); (4) the frontotemporal group [7].

Alzheimer disease (AD) is the most common form of dementia, comprising up to 80% of cases; however, not all studies distinguish AD from all-cause dementia. The estimated prevalence of all-cause dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, with North America falling between at 6.4%. Currently, over 46 million individuals live with dementia worldwide and this number is projected to increase to 131.5 million by 2050 [1].

Vascular dementia is regarded as the second most type of dementia [7]. The cardinal features of vascular dementia include history of stroke, fluctuating course, focal neurological symptoms, wide-based gait, and the presence of arteriosclerotic risk factors such as hypertension [8]. Of these features, Kotsoris et al. found that LUTS, reported by 50% of patients, frequently preceded the development of dementia by 5 years or more. Similarly, gait disturbance, noted in 24%, preceded the development of dementia by 2 years or more [9]. Post-stroke dementia (PSD) or post-stroke cognitive impairment (PSCI) may affect up to one third of stroke survivors.

Table 61.1 Causes for dementias [2–6]

Neurodegenerative - e.g. Alzheimer's dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease with dementia
Vascular - e.g. multi-infarct dementia, strategic infarct
Infections - e.g. Creutzfeld Jakob disease, syphillis, Whipple's disease, herpes encephalitis and other viral encephalitides, chronic meningitis, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis
Toxins - e.g. alcohol
Normal pressure hydrocephalus
Structural pathology - e.g. tumour
Inflammatory disorders - e.g. Multiple sclerosis, vasculitis, non-vasculitic autoimmune encephalopathies
Metabolic-related dementias - e.g. B12 deficiency, thyroid disease, parathyroid disease

PSD has been proposed as a label for any dementia following stroke in temporal relation [10]. Stroke is a leading cause of disability [11]. Research and interventions have historically focused on physical disabilities, while cognitive impairment—an important aspect for stroke survivors—has been rather neglected [12, 13]. Even minor stroke affects daily functioning, executive functions, and cognition, consequently affecting participation, quality of life, and return to work [13]. Stroke survivors are at increased risk of developing cognitive impairment. Obviously, the acute tissue damage may affect cognition. Nevertheless, despite prospective data being available, results are conflicting and the direct cognitive effect of a stroke event beyond the cognitive decline associated with age and vascular risk factors remains poorly understood. Physical impairments tend to improve, to a greater or lesser degree, following stroke; however, for reasons which remain unknown, cognitive impairments progressively worsen.

The pathognomonic pathology in Lewy body dementia (LBD) is an abnormal aggregation of the protein α-synuclein, referred to as a Lewy body, with the cytoplasm of the neurons. Besides cognitive decline, common symptoms of LBD are visual hallucinations, sleep disturbance, autonomic dysregulation, fluctuating attention, depression, and Parkinson

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_61

like symptoms of bradykinesia, rigidity, and tremor [1]. Clinically, LBD is distinguished from PDD by onset of dementia before or within the first year of onset of parkinsonism. Autopsy studies suggest that LBD accounts for 15–25% of dementia cases, making it the third most common type of dementia [14].

Unlike previously discussed dementias, frontotemporal dementia (FTD) is most prevalent among individuals aged 60–69 years, with roughly 13% having onset when younger than age 50 [15]. Younger onset may be due in part to heavy genetic loading for FTD, with up to 50% of cases being familial and up to 40% autosomal-dominant in nature [15]. Clinical presentation of frontotemporal dementia is usually heterogeneous. Progressive behavioural impairment and decline in executive functions are not uncommon [1].

Lobo et al. compared the age- and sex-specific prevalence of dementia, AD, and vascular dementia (VaD) across European population-based studies of persons 65 years and older [16]. Data from these studies were also pooled to obtain stable estimates of age- and sex-specific prevalence. A total of 2346 cases of mild to severe dementia were identified in 11 cohorts. Age-standardized prevalence was 6.4% for dementia (all causes), 4.4% for AD, and 1.6% for VaD. The prevalence of dementia increased continuously with age and was 0.8% in the group age 65–69 years and 28.5% at age 90 years and older. The corresponding figures for AD (53.7% of cases) were 0.6% and 22.2%, and for VaD (15.8% of cases), 0.3% and 5.2%. Variation of AD prevalence across studies was greatest for men. In the VaD subtype, a large variation across studies was observed, as well as a difference in prevalence between men and women that was age dependent. Dementia is more prevalent in women, and AD is the main contributor to the steep increase of prevalence with age.

More recently, de Pedro-Cuesta et al. [17] studied the prevalence of dementia in Spain (people aged 70 years and above). The survey included Central and North-Eastern Spanish sub-populations obtained from nine surveys and totalled 12,232 persons and 1194 cases of dementia (707 of Alzheimer's disease, 238 of vascular dementia). Prevalence of dementia and Alzheimer's disease in Central and North-Eastern Spain is higher in females, increases with age, and displays considerable geographic variation that may be method-related. People suffering from dementia and Alzheimer's disease in Spain may approach 600,000 and 400,000 respectively [17].

61.2 Prevalence of LUTS in Patients with Dementia

Urinary incontinence (UI) and Alzheimer's disease (AD) are common in the elderly population and have increased rapidly in recent decades [18]. It is difficult to distinguish LUT problems caused by bladder aging from those due to other concomitant diseases [19]. It has been shown that in geriatric patients with dementia, incontinence is much more frequent than in non-demented patients [20, 21]. Grant et al. [22] extracted data on 54,816 people aged 60–89 with dementia and an age-gender stratified sample of 205,795 people without dementia from 2001 to 2010 from The Health Improvement Network (THIN), a United Kingdom primary care database, demonstrated that compared to those without dementia, those with dementia were approximately three times more likely to report urinary incontinence [22].

Urinary incontinence and its prevalence have been the focus of most studies on LUTS in dementia, which relied on both patient and caregiver reports. Possibly, due to differences in patient selection among these studies, incontinence prevalence rates have varied considerably [2]. Overall, urinary incontinence affects around 50% of men and 60% of women with dementia, inevitably occurring in advanced stages of disease [18–20].

Alzheimer's disease (ALD) is the most common type of dementia in clinical and autopsy surveys. In patients with ALD, the prevalence of UI ranges from 23 to 48% [21, 22]. The onset of incontinence usually correlates with the disease progression [23]. Male to female ratio of dementia related incontinence was found to be 1:15.

However, symptoms of an overactive bladder (OAB) occur more commonly in dementia with Lewy bodies (DLB) and vascular dementia (48%), than in patients with Alzheimer's disease (AD) (40%) [18, 22]. In addition, the association of severe cognitive decline and urinary incontinence may be useful in differentiating Alzheimer's disease versus Lewy bodies disease. Urinary incontinence is associated with severe cognitive decline in pure Alzheimer's disease, but usually precedes significant cognitive impairment in diffuse Lewy bodies disease. This temporal pattern of cognitive decline and incontinence could be useful in differentiating these two subtypes of dementia [24] (Table 61.2).

LUTS have been reported in 93% of the patients with idiopathic normal pressure hydrocephalus (NPH). In this group, storage symptoms were more common than voiding symptoms (93% versus 71%). The most frequent LUTS were urgency (64%), frequency (64%) and incontinence (57%) [25].

Table 61.2 Urodynamic findings in patients with Lewy bodies disease, Parkinson and Alzheimer's disease [23]

	n	Cystometric bladder capacity (cc)	Max. detrusor pressure	Detrusor overactivity
LBD	12	**254 ± 185**	**38.5 ± 33.7**	**11 (92%)**
PD	13	**256 ± 76**	**42.2 ± 19.4**	**6 (46%)**
AD	10	**297 ± 154**	**45.8 ± 21.5**	**4 (40%)**
p		**0.97**	**0.21**	**0.02**

LBD Lewy bodies' disease, *PD* Parkinson's disease, *AD* Alzheimer's disease

61.3 Prognosis of Lower Urinary Tract Dysfunction in Patients with Dementia

61.3.1 Plateauing in Alzheimer's Disease

In Alzheimer's disease (AD), a plateau refers to a patient's remaining on a mild level of cognitive decline for more than two years. Survival curves (Kaplan-Meier method) showed that patients with plateauing reached several end-points such as very severe functional or cognitive impairment, urinary incontinence, and death significantly later than patients with progressive illness ($p < 0.04$). Patients with plateauing showed a smaller cognitive loss ($p < 0.01$) in terms of the mean annual rate of progression of mental decline. Patients who were plateauing in an early stage of Alzheimer's disease have been reported to have a more favourable course [26].

61.3.2 Lumbar Puncture and Shunt Operation in Normal Pressure Hydrocephalus Associated Dementia (NPHD)

Lumbar puncture and removal of 50 mL CSF has been shown to improve detrusor overactivity temporarily in NPH, and abolished by shunt operation. Urodynamic testing after lumbar puncture may predict the outcome of a shunt operation in cases of normal pressure hydrocephalus [27].

Urodynamic testing after lumbar puncture may predict the outcome of a shunt operation in these cases [2]. According to Sakakibara et al., a positive spinal tap test may predict successful outcome of shunt surgery, and the recovery rate of bladder function after shunt surgery ranges 30–70% of patients [28].

61.4 Management of LUTS in Patients with Dementia

LUTS in dementia patients can be caused by the dementia itself, by the neurological and urological pharmacotherapy, and by the ageing bladder or comorbidities [7].

61.4.1 Conservative Management

Urinary incontinence in Alzheimer's disease patients is frequently associated with cognitive impairment, suggesting its central nervous system origin. Therefore behavioural therapy, toilet training and prompted voiding would be most useful treatment modalities for this type of incontinence [7].

Behavioural therapy, including toilet training and prompted voiding, is useful and should be started early to induce reflex behaviour, which can be used later, when dementia progresses (going to the toilet = micturition/defecation; glass of water = drinking). Antimuscarics (**see* Sect. 4.2 'Medical Treatment') may enhance behavioural therapy, especially when the bladder capacity is reduced [23, 24].

Hutchinson et al. suggested that caregivers of patients with Alzheimer's disease should study the toileting behaviours. This would permit them to provide physical and cognitive assistance while attempting to avoid accidents and catastrophic events [25]. The conservative treatment should be tailored to individual patient needs and disease status, taking into account factors like mobility, cognitive function and general medical condition [26]. It has been demonstrated that prompted voiding decreases incontinence episodes in the short-term [27].

Patients with vascular dementia, especially those with restricted mobility, may benefit from individualized treatment strategies, which include:

- *Toiletting*
- *Antimuscarinics*
- *Improvement of mobility (physical therapy)*
- *Intermittent (self- or third-party-) catheterization when postvoid residual urine (PVR) is over 50% of functional bladder capacity is present, due to detrusor underactivity.*

61.4.2 Medical Treatment

First-line treatment for symptoms of the overactive bladder comprises behavioural therapy and antimuscarinics [2]. The ability of antimuscarinics to cross the blood–brain barrier and to be bound to the M1-receptors in the brain varies- oxybutynin, for example, permeates the blood–brain barrier with relative ease and also binds to the M1-receptors. A placebo-controlled study documented the deterioration of short-term memory, in an amount that corresponds to brain ageing over 10 years, when 10 mg of oxybutynin ER was described during 3 weeks [28]. Trospium chloride, however, is relatively impermeable to the healthy blood–brain barrier, as demonstrated by Staskin et al. in a group of healthy people above the age of 70 [29]. Darifenacin and solifenacin do cross the blood–brain barrier, but are less bound to M1-receptors, and therefore is associated with fewer CNS side effects than could be expected [2]. Propiverine, respectively its main metabolite, crosses the blood–brain barrier only to a minor extent [30]. However it must be remembered that evidence supporting these considerations in clinical practice is limited [31] and caution is advised when using an antimuscarinic agent in the susceptible neurological patient.

In general, antimuscarinic-induced cognitive impairment is considered reversible on discontinuation of antimuscarinic

therapy. However, a few studies suggest that use of medications with anticholinergic properties, such as antimuscarinics for the bladder, may be associated with an increased risk for dementia [31].

CNS side effects of antimuscarinics become crucial when they are prescribed to dementia patients already on acethylcholinesterase-inhibitors (AChEI). These medications are usually prescribed as first-line treatment to arrest cognitive impairment in conditions such as Alzheimer's disease, vascular dementia and dementia with Lewy Bodies. There is evidence to suggest that AChEIn may influence LUT functions, and Starr et al. reported that rivastigmine and donepezil (cholinesterase inhibitors) may worse urinary incontinence in Alzheimer's disease [32].

61.5 Conclusions

Different types of dementia cause LUTS at differing time points of the disease and need different therapeutic approaches. The degree of incontinence is strongly associated with patient's general status and ambulation. Although LUTS are highly prevalent in dementia patients, high-quality data to guide the choice of treatment strategies in this population are lacking. The extensive and aggressive therapy of LUTS should be reserved for those with good general status and ambulation. Behavioural therapy, including toilet training and prompted voiding, may be especially useful in patients with unawareness UI. The use of antimuscarinics that do not easily cross the blood–brain barrier or are more M2/M3 selective seems to be a rationale approach. On the other hand, current evidence suggests that antimuscarinics, especially oxybutynin, can be associated with cognitive worsening, due to antagonist effects at the M1 receptors of the brain. There are no studies on the use of beta-3 agonists for dementia patients so far. The extensive and aggressive therapy of incontinence in dementia patients should be reserved for patients with good general status and ambulation.

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Multiple Sclerosis

62

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62.1 Introduction

In 1868, Jean-Martin Charcot in Paris provided the first detailed pathology of "la sclérose en plaques," characteristic periventricular white matter lesions now appreciated as a pathological hallmark of multiple sclerosis (MS), the most common immune-mediated disease of the central nervous system (CNS) [1]. MS is characterized by exacerbations of neurological dysfunction due to inflammatory demyelination. Neurologic symptoms typically present in young adulthood and vary based on the site of inflammation, although disorders from hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and vision are common. MS occurs more frequently in women and its development is complex—genetics, hormones, geography, vitamin D, and viral exposure all play roles. Neuroimaging and cerebrospinal fluid (CSF) abnormalities, particularly oligoclonal band, help diagnosing early MS. In the past decade, there has been a remarkable expansion in disease modifying therapy for MS, but treatment of progressive disease (10% at onset) is still not established. Clinical features of MS include cognitive, gait, coordination, sensation, and bladder function. In particular, the treatment of bladder dysfunction remains a clinical challenge while it becomes a great disability in affected individuals and annual health care cost [1].

Neuromyelitis optica (NMO) spectrum disorder (NMOSD) is now recognized a novel disease entity akin to MS [2, 3]. In 1894, Eugene Devic in Lyon first described a series of patients with optic neuritis and myelitis, a monophasic manifestation and significant disability unlike multiple sclerosis. It was once felt that NMO and MS represented one disease entity, with variable phenotypes and expression. This notion, however, was replaced by the discovery NMO-IgG antibody that selectively binds aquaporin (AQP) 4 in 2004. Not only optic neuritis and myelitis, but also white matter disease/encephalitis etc. may occur with AQP4, thus these diseases are coined NMOSD. Further evidences suggest that NMOSD is distinct with respect to immunopathogenesis and suitable treatment. Frequency of MS vs. NMO is thought to be MS dominant in European/North America, while NMO dominant in Asia [4, 5]. More recently, myelin-oligodendrocyte glycoprotein (MOG)-IgG has been identified. MOG disease is now being separated from MS and NMOSD [6]. Clinical spectrum of MOG disease also covers optic neuritis, myelitis, and acute disseminated encephalomyelitis (ADEM) [6]. Therefore, bladder dysfunction might have often occurred in NMOSD and related diseases, while only limited literature is available.

This article reviews bladder dysfunction in MS, NMOSD, ADEM (monophasic, acute onset of encephalitis and myelitis) [7]. acute immune-mediated myelopathy as a localized form of ADEM [8, 9], and a newer concept 'meningitis-retention syndrome (MRS)' as a mild form of ADEM [10] with particular reference to lower urinary tract symptoms (LUTS), urodynamic finding and sphincter electromyography (EMG), and patient management.

62.2 Multiple Sclerosis

62.2.1 Bladder Dysfunction Is Common MS

Several control studies indicated the frequency of lower urinary tract symptoms (LUTS) in MS patients being up to 70% [11, 12]. LUTS in MS patients comprise storage and voiding symptoms, or both. Storage symptoms include overactive bladder (urinary urgency, usually accompanied by urinary frequency), and in advanced cases, urinary incontinence of urgency type. Stress urinary incontinence is rare in neurological diseases, since it derives from pelvic floor weakness or sphincter weakness (the latter occasionally occurs from sacral cord lesion). Overflow incontinence secondarily occurs after large post-void

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_62

residuals. Nocturnal frequency (nocturia) comes from not only neurogenic OAB, but also from insomnia and nocturnal polyuria (caused by mild cardiac failure [increased brain natriuretic protein (BNP) of cardiac origin], kidney dysfunction, postural hypotension, and rarely hypothalamic lesions (loss of nocturnal increase in arginin vasopressin of central origin)). Nocturnal polyuria can be assessed by bladder diary. These storage symptoms significantly affect the quality of life in MS patients. Voiding symptoms include hesitation, poor stream, difficulty urinating and urinary retention. However, post-void residual (PVR) is often not perceived by patients; therefore objective ultrasound measurement is important. Large PVR may lead to recurrent pyelonephritis, kidney dysfunction and morbidity [11, 12].

62.2.2 Both Overactive Bladder and Large Post-Void Residuals Occur in MS

Studies have shown that MS patients have both overactive bladder and large PVR, and the quality of life (QOL) index in MS patients was significantly higher (i.e., worse) for bladder dysfunction than that in controls. Many of them show large PVR urine volume > 100 mL.

What is the underlying mechanism for both overactive bladder and large PVR in MS patients? Since MS is a progressive immune-mediated disease that affects multiple CNS regions, MS patients may have a wide range of urodynamic abnormalities that may change with progression of the illness. Videourodynamics allows us to assume the site of lesions, and sphincter EMG enable us to assess particularly the lumbosacral cord functions. Neuroimaging and pathology studies showed that the commonly affected regions in MS are: hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and optic nerves. Among these, medial/prefrontal/insular cortex [13] (total brain volume [14]) (basal ganglia, hypothalamus), cerebellum [13] brainstem (midbrain [13, 15] pons [13, 16, 17]) and cervicothoracic spinal cord [14, 17] are all relevant to micturition function. Among these, brain lesions cause detrusor overactivity; sacral/peripheral lesions cause detrusor underactivity; and partial spinal cord lesions show a complex bladder behavior, and the spinal cord is very often affected in MS patients. This bladder behavior in spinal cord lesion is called DHIC, detrusor hyperactivity with impaired contraction, i.e., detrusor overactivity during bladder filling due to a novel C-fiber mediated micturition reflex, while detrusor underactivity during voiding due to damaged bladder descending pathway. This may accompany unrelaxing sphincter (also called DSD, detrusor-sphincter dyssynergia) (Fig. 62.1). Therefore, we should treat MS patients for not only OAB by anticholinergic medication etc., but also for large PVR by clean, intermittent catheterization (CIC) together. Sphincter electromyography (EMG) allows us to see whether sacral plaques are present in MS patients. Koutsis and colleagues studied relationship between LUTS (particularly OAB) with serum and cerebrospinal fluid (CSF) in MS patients [18]. They found low CSF 5-hydroxyindole acetic acid (5-HIAA, serotonin metabolite), and low

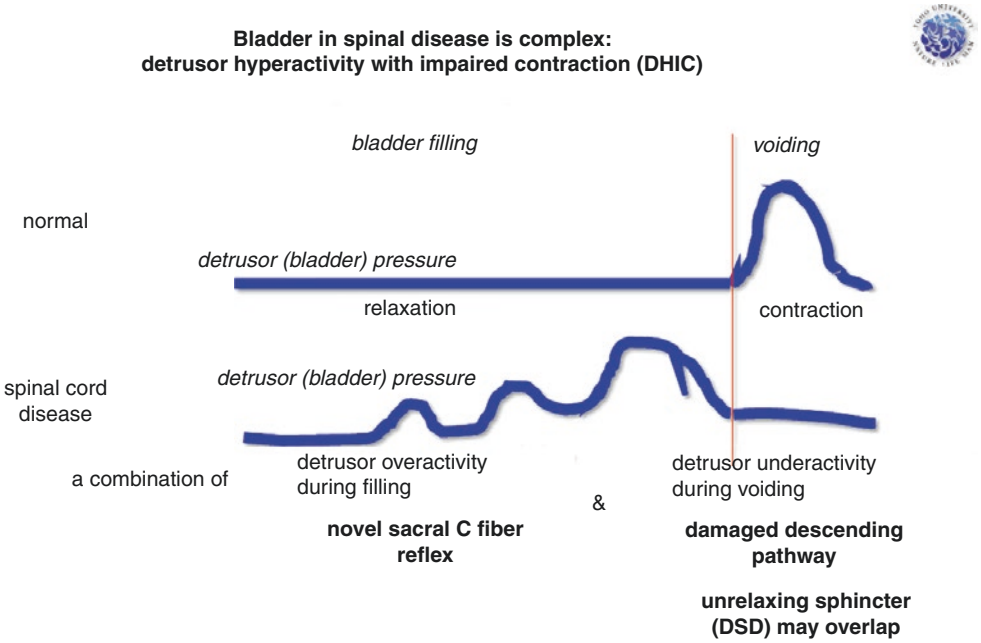

Fig. 62.1 Bladder in partial spinal cord disease is complex: a common cause of urinary symptoms in patients with MS. Both storage and voiding symptoms in patients with MSA were significantly worse than age matched controls. Particularly they had a significantly higher prevalence of voiding symptoms, particularly retardation in initiating urination (hesitancy) than the controls

serum cortisol. What do these findings mean is a debate, but it is postulated that brainstem raphe nucleus (source of serotonin, which suppresses the micturition reflex) might be affected in MS patients [18]. Hypothalamo-pituitary-adrenal axis (HPA axis) is a major source of serum cortisol (cortisol increased in depressive/stress patients). Since HPA axis receive input from the raphe, it may change in those patients.

There are experimental studies that simulate bladder dysfunction in MS, i.e., experimental autoimmune encephalomyelitis (EAE). Some studies showed peripheral bladder changes [19], whether or not they are secondary to CNS lesions. There seem some limitations in these studies, because EAE may produce severe bladder inflammation that is not seen in clinical MS [20]. EAE studies have shown that bladder correlated with motor [21–23]; and increased descending inhibitory (via glycine and GABA)/excitatory control for detrusor under/over-activity [22]. These findings implicated future bladder treatment/prevention in MS patients.

62.2.3 Management of Bladder Dysfunction in MS

There is a United Kingdom (UK) consensus on the management of the bladder in MS as edited by Clare Fowler [24] (Fig. 62.2). This consensus recommendations can basically be applied to the majority of MS patients. It was agreed that successful management could be based on a simple algorithm which includes using reagent sticks to test for urine infection and ultrasound measurement of the post-void residual (PVR) urine volume. This is in contrast with published guidelines which recommend cystometry. If treatment fails for OAB and large PVR, there seems to be a place to perform cystometry. Throughout the course of their disease, patients should be offered appropriate management options for treatment of incontinence, the mainstay of which is antimuscarinics or selective beta-3 adrenergic receptor agonists, in combination, if necessary, with clean intermittent self-catheterization (CIC). The treatment options offered to a patient should reflect the severity of bladder dysfunction, which generally parallels the extent of neurologic disease (Fig. 62.3) [11, 12, 24]. Physiotherapy [25–27] desmopression [28], tibial nerve stimulation [27] detrusor injections of botulinum toxin A [29] can also be options. However, beyond a certain point, incontinence may become refractory to all treatment options and it is at this stage that a long-term indwelling catheter should be offered. These treatments may prevent recurrent pyelonephritis and kidney dysfunction in the patients [30]. Future treatments may include sacral neuromodulation [31, 32] and medical cannabis [33].

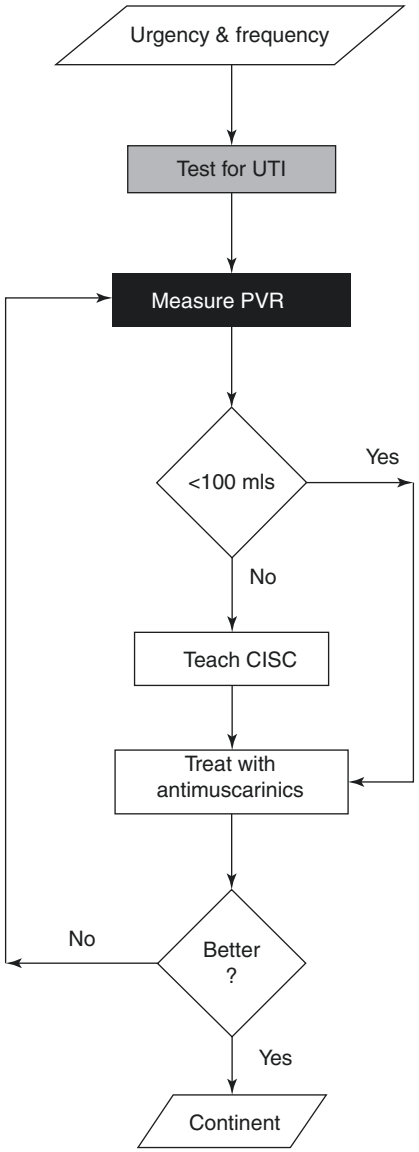

Fig. 62.2 Management algorithm for patients with multiple sclerosis presenting with urinary tract symptoms. *CISC* clean intermittent self catheterisation, *PVR* post void residual volume, *UTI* urinary tract infection. Reprint with permission from Franken et al. [23]

62.3 Neuomyelitis Optica Spectrum Disorder (NMOSD)

62.3.1 Bladder Dysfunction Is Not Uncommon in Neuromyelitis Optica (NMO)

Since spinal cord is the major site of lesions in NMOSD, bladder dysfunction might have often occurred in this disease, while only limited literature is available. Yamamoto et al. [34] studied 14 NMO and 34 MS patients by a lower urinary tract symptom (LUTS) questionnaire; and found that LUTS were more severe in NMO than MS, and LUTS might occur independently from motor/other neurological disabili-

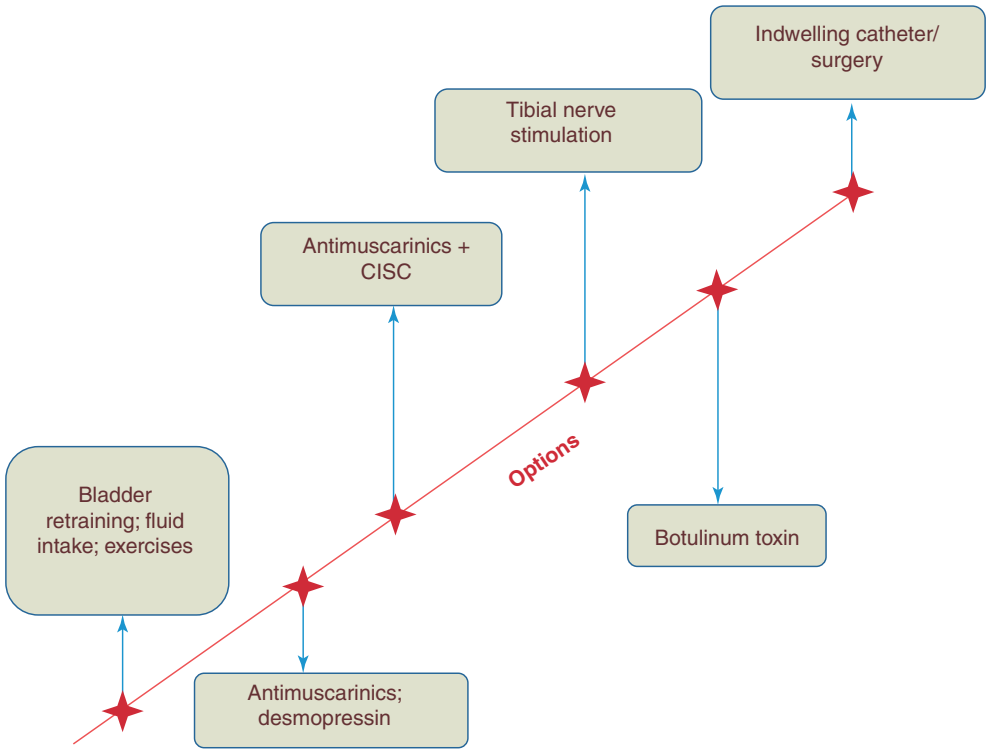

Fig. 62.3 Management algorithm for patients with multiple sclerosis presenting with urinary tract symptoms. *CISC* clean intermittent self catheterisation, *PVR* post void residual volume, *UTI* urinary tract infection. Reprint with permission from Phé et al. [11]

ties. Mutch et al. [35] studied 60 NMO by a LUTS questionnaire; and 78% had LUTS, 35% of them disappeared but in the remaining 65%, they persisted after resolution of first myelitis episode. De Carvalho et al. [36] urodynamically studied 30 NMOSD. They found detrusor overactivity (DO) alone in six (20.0%), DO and detrusor-sphincter dyssynergia (DSD) in 11 (36.6%), and DSD alone in seven (23.3%), while storage and voiding phases are not clearly separated. These findings seemed almost the same with those with MS. Furlana [37] and Dimitrijevic [38] showed that NMO can cause autonomic dysreflexia due to neurogenic bladder dysfunction.

Management of bladder dysfunction in NMO can be done according to that of MS, since the spinal cord is the major site of lesions in this disease as well.

62.4 Acute Disseminated Encephalomyelitis (ADEM)

ADEM is an immune-mediated demyelinating central nervous system (CNS) disorder with predilection to childhood [7]. ADEM is akin to MS; occurrence often postinfectious, but the differences include mostly monophasic, acute onset, and distinct pathologies. MRI of ADEM typically demonstrates white matter lesions of the brain and the spinal cord, and involvement of thalamus and basal ganglia may occur. However, in some cases ADEM presents with aseptic meningitis alone [39]. CSF analysis reveals a mild pleocytosis and elevated protein, but is often negative for oligoclonal band. The role of biomarkers, e.g., autoantibodies like anti myelin oligodendrocyte glycoprotein (MOG) is currently under debate. After immunotherapy such as steroid pulse therapy, outcome of ADEM is generally favorable, but cognitive deficits may persist in younger patients.

Patients with ADEM commonly have LUTS, which varies from urinary retention to urgency incontinence [40–42]. LUTS appears to be related to pyramidal tract involvement, and most probably reflects the severity of the spinal cord lesion. Urodynamics commonly show detrusor overactivity in the storage phase; and detrusor underactivity often with detrusor-sphincter dyssynergia (DSD) (reflecting a suprasacral spinal cord lesion); and neurogenic motor unit potentials in sphincter EMG in some patients (reflecting a conus lesion). Some cases of ADEM presented with LUT dysfunction alone, either initially, or as the only remaining consequence of the disease, thus suggesting that LUT innervation was selectively vulnerable in these cases [41, 43]. In some cases, abnormal F-waves were recorded, suggesting conus or a radicular lesion. Jayakrishnan [44] also showed that ADEM can cause autonomic dysreflexia due to neurogenic bladder dysfunction.

Management of bladder dysfunction in ADEM can be applied according to that of MS, since the spinal cord is one of the major sites of lesions in this disease as well.

62.5 Acute Immune-Mediated Myelopathy

Acute myelopathy is common in both general and neurologic practice. The differential diagnosis includes compressive, structural, infectious, vascular, neoplastic, metabolic, toxic, genetic, and traumatic etiologies. Among these, noninfectious

inflammatory (immune-mediated) myelopathies represent a localized form of ADEM, which is a treatable group of disorders [8, 9]. Most patients share common disabilities, e.g., motor, sensory, and bladder dysfunction. Of these, bladder dysfunction needs particular care at the acute phase. In the most extensive cases, acute immune-mediated myelopathy simulates spinal cord injury, i.e., paraplegia, sensory loss below the level of lesion, and loss of bladder sensation and urinary retention. MRI of such cases demonstrates transverse lesion. In contrast, some cases of acute myelopathy presented with LUT dysfunction alone, either initially, or as the only remaining consequence of the disease [45]. MRI of such cases shows localized lesions in the lateral funiculus, where the spinal descending pathway for micturition exists [46, 47]. Urodynamics commonly show detrusor overactivity in the storage phase; and detrusor underactivity often with detrusor-sphincter dyssynergia (DSD) (reflecting a suprasacral spinal cord lesion) [48–50]. Canon [51] showed that acute myelopathy can cause autonomic dysreflexia due to neurogenic bladder dysfunction. Management of bladder dysfunction in acute myelopathy can be applied according to that of MS.

62.6 Meningitis-Retention Syndrome (MRS)

In 2005, three adult patients who developed acute co-occurrences of aseptic meningitis (AM) with urinary retention that lasted for several weeks were reported; this syndrome was named 'meningitis-retention syndrome (MRS) [10, 52]. Although one of these three patients had a mild disturbance of consciousness, the other two had no other neurological abnormalities except for slightly brisk lower extremity deep tendon reflexes. MRS has been reported mostly in Japan. However, it has been recently reported also in other countries. Recently, frequency of MRS among AM is reported to be 8% [53]. The duration of total illness and hospitalization in MRS was longer than that in AM without urinary retention. Average latencies from the onset of meningeal irritation to urinary symptoms were 0–8 days. Therefore physicians should aware that urinary retention can follow after admission in AM patients. The duration of urinary retention in MRS was mostly 7–14 days, lasting up to 10 weeks.

Mild ADEM is considered an underlying mechanism of MRS, because some patients show elevated myelin basic protein in the cerebrospinal fluid (CSF) and a reversible splenial lesion on brain MRI. As it is observed in ADEM, antecedent/comorbid infections or conditions with MRS include Epstein–Barr virus, HSV2, West Nile virus, listeria, *Angiostrongylus cantonensis*, Vogt–Koyanagi–Harada disease, and herbal medicine use. The CSF examination of the patients showed a mononuclear pleocytosis of 38–370/mm[3], normal to increased protein content (up to 260 mg/dL), and normal to mildly decreased glucose content (up to 33% of that in the serum). Recently, elevated CSF adenosine deaminase (ADA) levels or decreased CSF/serum glucose ratio may be predictive factors for MRS development [53] (Fig. 62.4).

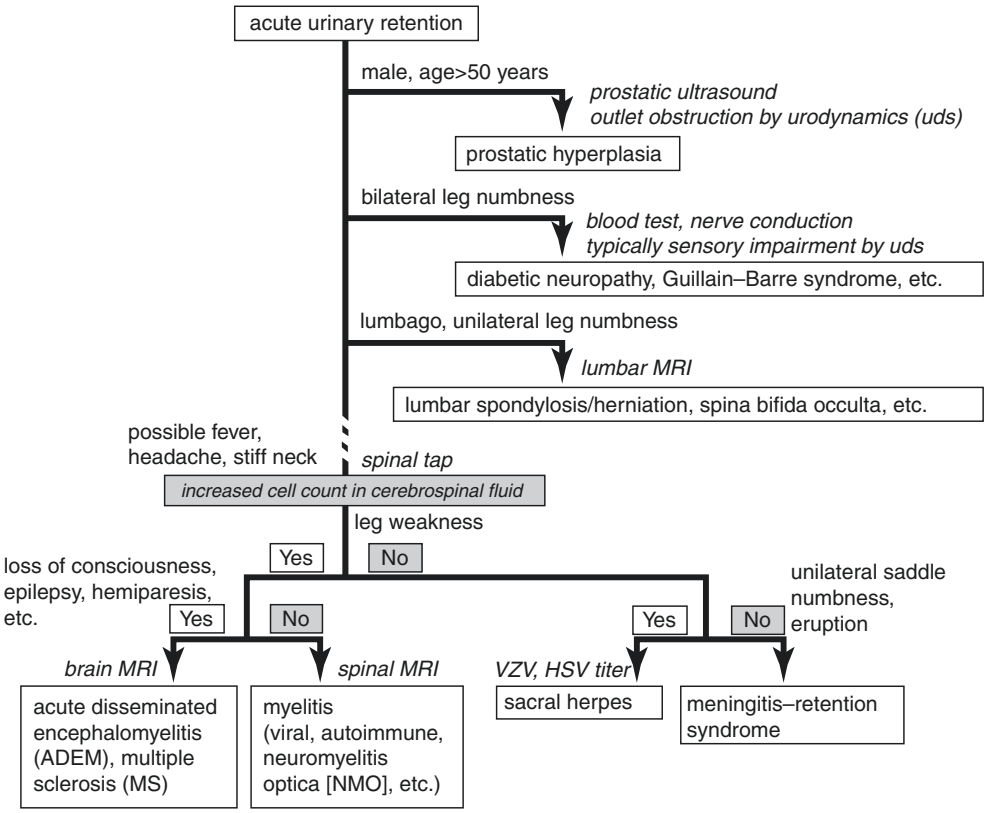

Fig. 62.4 Algorithm to diagnose meningitis–retention syndrome and related conditions. *yo* years old, *MRI* magnetic resonance imaging, *HSV* herpes simplex virus, *VZV* varicella zoster virus. Reprint with permission from Sakakibara et al. [10]

Urodynamics show that all patients examined had detrusor underactivity when on retention, and two patients had an unrelaxing sphincter together [51, 53–60]. Detrusor underactivity originates from various lesion sites along the neural axis; most commonly, PNS lesions are observed. However, CNS lesions that affect the spinal cord or the brain can also cause detrusor underactivity, which is seen in the acute-shock phase of patients. Tateno et al. encountered a man with MRS in whom a urodynamics was performed twice. In that case, an initially underactive detrusor became overactive after a 4-month period, suggesting an upper motor neuron bladder dysfunction [61].

The term "Elsberg syndrome" is occasionally assigned to urinary retention of diverse etiologies. In contrast, Kennedy, Elsberg, and Lambert (1913) reported five cases of pathology-demonstrated cauda equina radiculitis [62]. Their clinical/pathological features were: rare CSF abnormalities; no clinical meningitis; a subacute/chronic course; presentation with typical cauda equina motor-sensory-autonomic syndrome; Wallerian degeneration of the spinal afferent tracts; and mild upper motor neuron signs. All these are different from those of MRS. The exact cause of these cases are uncertain. However, they resemble paraneoplastic/autoimmune lumbosacral radiculoplexus neuropathy.

While MS, NMOSD, ADEM and AM need steroid pulse or extensive immune therapy, MRS has a benign and self-remitting course, and the effectiveness of immune treatments (e.g., steroid pulse therapy) remains unclear, although such treatments may shorten the duration of the disease. Management of acute urinary retention is necessary to avoid bladder injury due to overdistension. Since AM is common in general/neurological practice, MRS is more common than was previously believed, and do not miss such MRS patients.

62.7 Summary

Urinary dysfunction is common in NMOSD, ADEM, AM and MRS, immune-mediated CNS disorders particularly affecting the spinal cord. Spinal cord lesion typically leads to motor, sensory, and bladder autonomic dysfunction, and urodynamic study may reveal DHIC (detrusor overactivity [overactive bladder with/without incontinence] during bladder filling, while detrusor underactivity [large post-void residuals/urinary retention] during voiding) with DSD (unrelaxing sphincter on voiding). Because of this, we should care for both overactive bladder and post-void residuals; e.g., the former antimuscarinics etc., and the latter clean, intermittent self-catheterization. In MS, consensus guideline is also available. These management may allow maximizing the quality of life in the patients.

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Spinal Cord Injury

63

Hazel Ecclestone and Rizwan Hamid

63.1 Introduction/Epidemiology

Spinal cord injury (SCI) is a sudden devastating life-changing event. This may be a consequence of trauma, infection, vascular or iatrogenic injury. Once the acute phase is over, neurological consequences are usually stable and persist lifelong. The severity of SCI is reflected in the degree of paralysis and sensation loss as well as the (in)ability to perform activities of daily living, and is classified by the American Spinal Injury Association (ASIA) impairment scale [1].

The life expectancy of patients with SCI continues to increase. Those who sustain an injury between the ages of 25 and 34 can expect to live on average 38 years after injury, with 43% surviving at least 40 years [2]. The most common cause of death in contemporary series is diseases of the circulatory (40%), and of the respiratory system (24%), in contrast to primarily renal mortality in earlier series [3]. The epidemiology of SCI has also changed over time, with the incidence of women with traumatic SCI increasing, and now standing at a male:female ratio of 4:1 [4].

Injuries can also be described as either complete, or incomplete. A 'complete' lesion implies that all function below the level of the injury is lost, whereas in an incomplete lesion some of the motor and sensory function below the level of the lesion is preserved. The most common injury group is incomplete quadriplegia (28%) followed by complete paraplegia (26%); complete quadriplegia (24%) and lastly incomplete paraplegia (18%) [1]. Autonomic function is also almost always impaired in SCI, but the current classification system this is not reflected, recently it has been proposed to adapt the classification system to reflect alterations in autonomic function including that of the lower urinary tract, bowel and sexual function [5]. Pelvic organ dysfunction not only has an adverse outcome on patients quality of life, but untreated neuropathic bladder dysfunction can lead to upper urinary tract damage and ultimately death.

63.2 Bladder Dysfunction

After SCI bladder dysfunction typically occurs in two phases, the initial spinal shock, followed by the stable chronic phase. The level of spinal cord injury also determines the type of dysfunction that is typically seen (suprasacral vs. sacral cord lesions).

63.2.1 Spinal Shock

It is characterised by depressed spinal reflexes below the level of injury, this phase begins in the initial period following the injury, and lasts a variable amount of time (from days to months) [6]. In terms of bladder function the detrusor is areflexic and the bladder acontractile. It is usually managed initially with an indwelling catheter, which is often urethral. Acutely following SCI fluid management and resuscitation contribute to difficult fluid balance and as such an indwelling catheter is often preferable. Once the patient has been haemodynamically stabilised, and no longer requires supplemental IV fluids then it is often appropriate to consider alternative forms of bladder management as soon as possible such as clean intermittent catheterisation (by the patient or carers). The patient should be encouraged to catheterise 'by the clock' every 3–5 h as sensation of bladder filling is compromised and one aims to keep the bladder volume below 500 mL.

63.2.2 Chronic Neurogenic Bladder Dysfunction

63.2.2.1 Supra-Sacral Bladder

In patients with SCI lesions above the cauda-equina (above L1–L2) with spastic paralysis, the cessation of spinal shock

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_63

and return of autonomic function is followed by the emergence of a spinal bladder reflex originating from the functionally isolated spinal cord segment. Higher centres (such as the pontine micturition centre) are important for the regulation of the urethral/bladder complex, and the co-ordination of storage and voiding phases are therefore lost. The resulting abnormalities usually seen are neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD).

Under normal situations, when micturition is to occur the control centre of the external urinary sphincter, Onufs nucleus (located S2–S4) is inhibited by the pontine micturition centre allowing simultaneous contraction of the detrusor and relaxation of the sphincter. When the connection to the higher centres has been severed (such as in SCI) however the 'guarding reflex' comes into play, and as the bladder progressively fills, the urethral sphincter tone increases. In the neurologically intact individual this reflex is designed to prevent leakage as bladder volume increases, but following a SCI the uncontrolled guarding reflex leads to progressive sphincter contraction along with detrusor contraction—so termed detrusor sphincter dyssynergia.

The combination of DSD and NDO means patients complain of both storage and voiding symptoms [8]. The bladder outflow obstruction caused by DSD can contribute to high bladder residual volumes and dangerously high intravesical pressure. Ambulatory status and completeness of injury and urodynamic findings are not necessarily correlated [9] and as such it is important to follow up all patients who have had an SCI regardless of their apparent degree of impairment.

63.2.2.2 Infrasacral Bladder

In lesions below the level of the cauda equina, or where the entire cord distal to the injury is damaged we typically see a 'infrasacral bladder'. The bladder in this situation is usually areflexic from the outset and does not regain contractility with time. The sphincter complex is also denervated and thus usually under-active, although the guarding reflex may be present in higher or incomplete lesions. Patients therefore typically present with difficulty emptying, poor flow and hesitancy and are commonly in retention with or without overflow incontinence. The bladder compliance may also be impaired and therefore intravesical pressures may be dangerously elevated.

63.3 Autonomic Dysreflexia

Autonomic dysreflexia (AD) is a medical emergency in patients with injuries at or above T6 who are prone to autonomic failure. In these patients there is a disconnection between the spinal sympathetic centres and supra-spinal controls [10] whereas the parasympathetic pathway runs largely outside the spinal cord. AD is a sudden and exaggerated response to a noxious stimuli occurring below the level of injury due to massive sympathetic discharge. AD is characterised by arterial hypertension and bradycardia, with the symptom constellation of headache, anxiety, profuse sweating flushing and piloerection above the injury and dry/pale skin below the injury [10]. If not recognised and treated promptly AD can have fatal consequences [11]. Triggering stimuli are most commonly distended bladder or bowel, but can also be due to pressure sores, sexual stimulation, skin irritation or infected toe nails. It can also be due cystoscopy or urodynamics. The severity of AD is related to the completeness of SCI (27% individuals with incomplete quadriplegia vs. 91% of those with complete quadriplegia) [10].

The best way to reduce the risks associated with AD is in prevention. Invasive urodynamic studies are a potent precipitant of AD in susceptible patients, and it is advisable to monitor blood pressure when performing urodynamics [12]. Furthermore, at the start of the procedure, it is advisable to check the rectal ampulla is empty of stool, and the bladder is filled at a slow fill rate with body warm saline [13].

If the patient does develop AD during a urological procedure, the patient should be sat up (to minimise the chance of hypertensive brain injury), and the cause must be quickly identified and removed (usually by bladder emptying). In the majority of cases this should resolve the AD. The guidelines of the consortium for spinal cord medicine recommend further treatment if systolic blood pressure continues to be above 150 mmHg in an adult. A short acting rapid onset antihypertensive should then be administered (such as sublingual nifedipine) [14].

63.4 Assessment of Bladder Function Following SCI

The key priority for the neuro-urologist is to protect the upper urinary tract (UUT). This involves initial assessment of UUT damage as well as a thorough assessment of risk factors that may predispose an individual to damage in future. The initial assessment is usually performed 3–6 months after initial injury and is repeated on a regular basis [13].

Patients often have different aims, primarily achieving social continence and quality of life and the skill of a neurourologist comes in adapting bladder management to the patient's disability, balancing both the aims of the patients with the need to protect the upper urinary tract. An initial quality of life assessment tool such as the validated questionnaire qualiveen should be completed at initial assessment and can be repeated to assess impact of changes in management [15].

Initial assessment of the patient should be holistic, not only focusing on storage and voiding lower urinary tract symptoms, but also on bowel and sexual function impairment. Red-flag symptoms are also important to identify and

investigate if necessary (pain, infection, haematuria and fever) [13]. It is also important to assess mental status and comprehension along with visual and hand function as these all will have a bearing on future treatment options.

Examination should document neurology as completely as possible including sensation and reflexes in the urogenital areas and anal sphincter function [13].

Patients with SCI should undergo ultrasound of the kidney, ureter and bladder (USS KUB) to assess for hydronephrosis and renal scars/stones, as well as blood chemistry, flow rate and residual and video-urodynamics (VUDS) (although if not available standard pressure flow studies can be used). Additional investigations such as dimethlymercaptosuccinic acid (DMSA) renography or mercaptoacetyltriglycine (MAG3) renograpgy, direct visualisation with cystoscopy and computerised tomography of the urinary tract may also be indicated depending on the initial history, examination and investigations.

Videourodynamic studies are considered the gold standard for the assessment of urinary tract function following SCI and give prognostic information about risk factors for subsequent damage to the UUT. This investigation is comprised of a filling and a voiding phase. The filling phase looks at bladder sensation, cystometric capacity, urethral activity, detrusor leak point pressure (DLPP) and presence of detrusor overactivity and screening shows bladder outline as well as presence of vesicoureteric reflux. The voiding phase reveals information about detrusor contractility, presence of DSD and screening reveals any urethral abnormalities and the location of any bladder outflow obstruction. A typical 'suprasacral bladder' urodynamic trace demonstrating DSD and NDO.

63.5 Follow-Up of Patients with SCI

Individuals with SCI are considered at high risk for renal deterioration for the entirety of their lifespan and as such regular lifelong follow up is recommended in international guidelines [13, 16]. A suitable follow up scheme would be annual USS KUB and VUDS evaluation, with increasing frequency if clinical symptoms change or risk factors such as DSD and impaired compliance are deteriorating (Table 63.1).

Table 63.1 Minimal follow-up requirements—adapted from EAU guidelines [13]

Investigation	Frequency	Grade
Urinalysis	At least once every 6 months	A
Ultrasound of the upper urinary tract, bladder status, post void residual	Every 6 months	A
Physical examination, blood biochemistry, urine microbiology	Annually	A
(Video-) urodynamics in patients without detrusor overactivity and normal bladder compliance	Every 2 years	A
(Video-) urodynamics in patients with detrusor overactivity, and/or low compliance	At least once a year	A

63.6 Potential Long Term Complications of Neuropathic Bladder

63.6.1 Renal Failure

Prior to the routine usage of clean intermittant catheterisation and aggressive bladder management of patients with SCI the prevalence of renal failure was 50%, and although this has deceased with time SCI patients are still five times greater than the general population to suffer from renal failure [17].

63.6.2 Stone Disease

The incidence of renal stones is higher than the general population in individuals with SCI, with a prevalence between 1.2 and 35% [18]. Bladder stones are also frequently seen in patients with SCI and are related to recurrent urinary tract infections as well as type of bladder management (indwelling catheter > intermittant catheterisation) [16] and urological surgery (e.g. augmentation cystoplasty).

63.6.3 Bladder Cancer

There is an increased risk of bladder cancer in patients with SCI over that of the general population, and the reported prevalence is between 0.1 and 10% [19]. The histology is squamous cell carcinoma in the majority of cases [20]. Non specific symptoms such as recurrent infections and incontinence should be promptly investigated as presentation is often insidious. Similarly haematuria should always be thoroughly investigated due to the possibility of malignancy.

63.7 Bowel Dysfunction

Neuropathic bowel is common in patients with SCI, characterised by constipation with or without faecal incontinence. Surprisingly, there are no guidelines as to the optimal management of bowel dysfunction following SCI. It is however prudent to consider conservative management prior to more invasive methods. The most effective management appears to be diet and oral fluid management advice, as well as a combination of oral and rectal drugs and physical interventions such as rectal irrigation/digitation with abdominal mas-

sage [21]. Transanal irrigation was particularly effective in an RCT when compared to conservative management improving both constipation and faecal incontinence scores, as well as health related quality of life scores [22].

63.8 Sexual Dysfunction

63.8.1 Males

Sexual dysfunction in both males and females with SCI is common. Around 40 of males are unable to attain an erection spontaneously, and over a third report anejaculation [23]. Patients with lesions above L2 typically can attain erections in response to reflex and psychogenic stimuli. First line treatment of erectile dysfunction (ED) in SCI patients is based on phosphodiesterase inhibitors (PDE-5). The reported ED improvement rate with sildenafil is more than 75% [24]. Should initial treatment with PDE5 inhibitors fail, then second line therapies are effective. Vacuum erection devices tend to have modest patient satisfaction rates, but intracavernosal injections are well tolerated with response rates in excess of 90% [25]. A penile prosthesis can be considered in refractory cases which have excellent patient satisfaction rates, but a significant complication rate of up to 10% [25].

As the majority of SCI patients have difficultly ejaculating, the most commonly employed technique to obtain semen is vibro-ejaculation, performed with a specially designed vibrator applied to the underside of the glans penis. In those with infrasacral lesions, vibro-ejaculation may not be successful and electroejaculation may then need to be considered. This is performed by using a transrectal electrical stimulation probe that directly stimulate the seminal vesicles. Electroejaculation is however an invasive therapy and there is a risk of rectal injury. It may require a general anaesthetic for those with incomplete lesions as it is painful. Semen parameters are often impaired even when erection and ejaculation are not impaired with the presence of retrograde ejaculation making sperm harvest more difficult [26]. Overall pregnancy rates however using combinations of the above techniques are 51% with a live birth rate of 40% [26].

63.8.2 Females

Literature on sexual dysfunction in females is limited. The neurophysiology of female arousal and orgasm is not fully understood, but female individuals with SCI have impaired ability to orgasm, with only 50% (c.f. 100% neurologically intact) of women with SCI able to achieve orgasm. Those with complete lower motor S2–S5 lesions are less likely to orgasm with only 17% being able to achieve orgasm compared with 59% of lesions at other levels [27]. There is little high quality evidence about fertility rates in females following SCI, but it is not felt to be as significantly impaired as in males [26].

63.9 Management of the Neuropathic Bladder

The management plan should be formulated in consultation with the multidisciplinary team, and aims are:

- Low pressure storage
- Maintain continence
- Upper tract protection
- Complete bladder emptying
- Maintain quality of life

Although achieving a normal urinary tract is the aim, one must acknowledge that this may not be possible due to the course and prognosis of the neurological disease.

63.9.1 Conservative Therapies

These include drugs, use of catheters and external collection devices.

63.9.1.1 Drugs to Decrease NDO

Neuropathic patients usually require higher doses of oral antimuscarinics to control NDO, albeit with increased side effects [28]. Oxybutynin has also been used intravesically with fewer side effects but has not been widely accepted due to the need for catheter instillation [29].

63.9.1.2 Drugs to Decrease Outlet Resistance

There are no drugs available to relax the external sphincter. However, selective and non-selective alpha blockers can be used to relax bladder neck and have been employed to facilitate bladder emptying and decrease the incidence of autonomic dysreflexia [30].

Intermittent Catheterisation (IC)

Popularised by Lapides, IC is performed by the patient (self) or by carers, 4–6 times per day. The patient should be motivated with good hand function and adequate mental capacity. Complications include urethral trauma with bleeding, false passages and urine infections [31].

63.9.1.3 Indwelling Catheters

These should be avoided long-term. Occasionally, however this maybe the only practical method of bladder management. There is controversy in the literature regarding the adverse outcome with long term catheterisation but overall this does not appear to lead to significant renal deterioration

[32]. The advantage of the suprapubic catheter is that the urethra is protected from cleavage and it is hygienically superior. Indwelling catheters increase the risk of bladder cancer as a result of chronic irritation and recurrent infection but there is no consensus as to the best method of screening these patients. Cystoscopy failed to detect any cancers in a 12 year follow-up study [33].

63.9.1.4 Assisted Emptying

Reflex voiding is generally not recommended especially in an upper motor neurone type bladder. Bladder contraction against a closed external sphincter secondary to detrusor external sphincter dyssynergia can lead to high bladder pressures resulting in obstruction to upper tract drainage or incomplete emptying causing recurrent infections and incontinence. However, in suitable patients this can be employed after external sphincterotomy or stenting of the sphincter. Similarly, bladder emptying by abdominal straining (Valsalva emptying) in a lower motor neurone type injury is not encouraged as this can lead to incomplete emptying and infections along with prolapse of the pelvic organs.

63.9.1.5 Rehabilitation

In selected patients a careful programme of timed voids with bladder re-training, life style modifications, pelvic floor exercises and biofeedback might be beneficial [34].

63.9.1.6 External Devices

Various collecting devices such as condom catheters can be used in males. However, as a significant number of patients can have altered sensations this has to be monitored carefully to avoid skin lacerations. In both sexes pads are an option if all other measures fail.

63.9.2 Surgical Treatment of a Neuropathic Bladder

The surgical options for treatment of a NBD are summarised in Table 63.2.

Table 63.2 Surgical management of NBD

Failure to store
Decrease detrusor contractility
Botulinum toxin A
Cystoplasty
Auto-augmentation
Increase outlet resistance
Artificial urinary sphincter
Slings
Bulking agents
Failure to empty
Enhance detrusor contractility
Sacral anterior root stimulator
Sacral neuromodulation
Decrease outlet resistance
External sphincterotomy
Stents (temporary & permanent)
Botulinum toxin – A
Procedures to circumvent bladder
Ileal conduit
Orthotopic bladder

63.9.2.1 Treatments to Decrease Detrusor Contractility

Botulinum Toxin A

Botulinum toxin A has been very successfully used to control NDO since been popularised by Schurch [35]. This has now become the mainstay of controlling NDO. It is a temporary treatment with effects lasting an average of 9 months. Repeat injections have been successful and no ultrastructural changes have been detected to date [36]. There have been reports of generalised muscle weaknesses especially with English Botulinum toxin A (Dysport) [37]. The approved dose is 200 U Botox mixed with 30 mL of normal saline injected intradetrusor at 30 sites sparing trigone [38].

Clam Cystoplasty

In patients with uncontrolled NDO refractory to other treatment, clam cystoplasty is successful in expert hands. The bladder is bivalved and bowel, preferably terminal ileum is used to increase the bladder capacity and decrease NDO. The 5-year success rate for continence and increasing bladder capacity is in excess of 90% [39]. However, there can be a number of short and long term complications [40].

Auto-Augmentation

Although some experts feel that auto-augmentation offers comparable results to cystoplasty [41] this is currently not the favoured option amongst majority of urologists.

63.9.2.2 Treatments to Increase Outlet Resistance

Bulking Agents

Success rates vary between 20 and 50% with collagen and polydimethylsiloxane [42, 43] and hence are used sparingly but do have a role in the infirm patient.

Slings and Tapes

The bladder neck slings have been used but mainly in paediatric population with success around 70% [44]. The main problems are failure and difficulty in catheterization due to the angulation of the urethra. Lately, transvaginal tape has been successfully used in the female neuropathic incontinence with about 60% success at 10 years [45].

Artificial Urinary Sphincter (AUS)

The most successful treatment of stress related urinary incontinence in a neuropathic patient is the use of an AUS. There are three components: peri-urethral cuff, pump in the scrotum and balloon in the retropubic space. Recent reports in the adult neuropathic population indicate long-term success rates of around 70%, but almost half require additional procedures [46, 47].

Bladder Neck Closure

This is used as a last resort and is combined with either a catheterisable stoma or a suprapubic catheter with success rates of around 75% [48]. The main disadvantage is irreversibility and loss of secondary access to bladder in case of failure to catheterise. In females this is performed vaginally and Martius fat pad is interposed between bladder neck and anterior vaginal wall to prevent fistulisation [49].

63.9.2.3 Treatments to Enhance Detrusor Contractility

A variety of techniques have been described to enhance detrusor contractility but only sacral anterior root stimulation (SARS) has stood the test of time [50]. This can only be performed for complete lesions as the stimulation is very painful. It will also stimulate the urethral sphincter but micturition occurs as the striated muscle relaxes faster than the smooth muscle. Although there is no need to CISC, posterior rhizotomy means loss of reflex erections. However by changing the parameters this technique can be used to induce erection and defecation [51].

Sacral Neuromodulation (SNM)

Neuromodulation is the process in which the influence of activity in one neural pathway modulates the pre-existing activity in another pathway through synaptic interactions [52]. A stimulator is surgically implanted in the buttocks (Fig. 63.1). This stimulates the appropriate nerves by using mild or moderate electrical impulses. This can help restore coordination between brain, pelvic floor, bladder or bowel and sphincter muscles [53], with increasing evidence in the literature that SNM suppress NDO, increases capacity and is reversible [54].

63.9.2.4 Treatments to Decrease Outlet resistance

External Sphincterotomy

If left untreated DSD leads to a complication rate of 50% including urosepsis, hydronephrosis, stones and reflux, which can all lead to deterioration of renal function [55]. External sphincterotomy is the gold standard for treating DSD, although often needs to be repeated. The complications include sepsis, bleeding and erectile dysfunction [56].

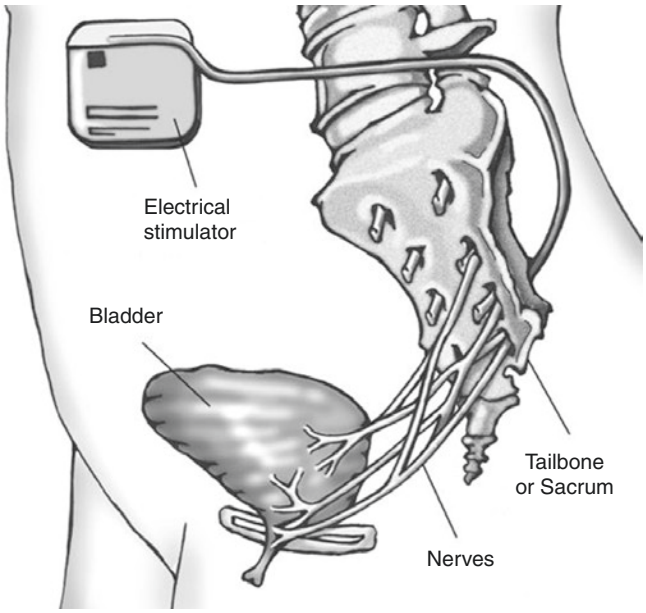

Fig. 63.1 A sacral nerve stimulator

A bladder neck incision might be necessary later on to overcome bladder neck dysnergia.

Urethral Stents

There are two main types of urethral stent; Memookath (temporary) and Urolume (permanent). They are both potentially reversible and require a shorter hospital stay [56] than sphincterotomy. The potential complications are migration, encrustation, blockage, bladder neck dyssynergia and incomplete emptying with development of AD [57]. A memokath stent can be inserted through a Urolume to overcome bladder neck dyssynergia.

Botulinum Toxin A

Lately, Botox injections have been used to treat DSD, however the effects are temporary and hence need to be repeated [58].

63.9.2.5 Treatments to Circumvent Bladder

Continent Diversion

This should be the first choice for diversion if the patient cannot (limited dexterity)/will not use their urethra. A mitrofanoff tube is fashioned from appendix, ileum or fallopian tube and is tunnelled into the ileocystoplasty augment, resulting in continence. The umbilicus is a cosmetically excellent exit site has a high stenosis rate [59]. Short-term continence rates are over 80% [60].

Incontinent Diversion

An ileal segment is usually used and patients require lifelong follow-up to detect complications including infections,

anastomotic stenosis, deterioration of renal function and metabolic disturbances [61]. Importantly, if the bladder has been left behind there is 30% chance of developing pyocystitis.

Undiversion

The development of better techniques to control incontinence and NDO have led to many long-standing diversions be successfully undiverted [62]. Increasingly, patients are more aware of body image and many who had diversion as a child might ask for a continent stoma later in life.

63.10 Conclusion

SCI is a multisystem disease and clinical presentation depends on the level and completeness of the lesion. The role of the neuro-urologist is to complete a thorough holistic assessment of a newly injured patient with SCI and tailor patient expectations and aims to ensure upper urinary tract protection is coupled with acceptable continence and low risk of urological complications. Regular follow up is of paramount importance, and any deterioration in parameters should trigger an alteration in bladder management. Furthermore as part of the holistic assessment and treatment of individuals with SCI, neuro-urologists should also require about bowel and sexual function, and instigate changes in management to improve patient's quality of life.

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Neurogenic Lower Urinary Tract Dysfunction in Children

64

Stuart B. Bauer

Abstract

In the last 40 years, the management of neuromuscular dysfunction of the lower urinary tract in children has undergone profound changes due to increased understanding and vast improvements in development of drug and surgical therapies. This chapter describes the current issues surrounding its prevalence, recent attempts at prenatal management, early postnatal lower urinary tract function, initial postnatal management, risk factors for upper urinary tract deterioration, reasons for prophylactic therapy that reduce compromises to renal function, assessment of sexual function as these individuals are surviving into adulthood and as such it plays an increasingly important role in their lives and finally, advances in the management of bowel dysfunction as that becomes paramount with affected patients surviving and wanting to become more engaged in society.

64.1 Introduction

Neuromuscular dysfunction of the lower urinary tract (LUT) arises from congenital or acquired conditions, the most common of which is a neural tube defect (NTD). Prior 1960, the outcome of children with NTDs was poor; <10% survived infancy [1]. Improvements in neurosurgical and urologic care have resulted in significant improvement in survival such that >85% now live into adulthood [1]. One prominent reason has been institution of clean intermittent catheterization (CIC) to prevent upper urinary tract deterioration [2]. A longitudinal cohort study revealed 1/3 of children died before 5 years of age, and 1/4 died before 40 years [3]. Death risks relate to higher neurologic levels [3]. As patients live longer, renal failure plays an important role in mortality; thus lifelong monitoring and management of the urinary tract in infancy is needed [4–6]. As children survive longer the challenges to achieving bowel and bladder continence [7, 8] and sexual function become paramount [9].

As noted, the most common cause of neurogenic bladder dysfunction in children is abnormal development of the spinal canal and spinal cord. NTDs have a worldwide incidence of 0.3–4.5 per 1000 births [10]. The latest estimate for occurrence of spina bifida (SB) in the United States (adjusted for maternal race and ethnicity) is 3.50 per 10,000 live births [11], correlating to about 1460 cases annually [11]. Children of Hispanic descent mothers have the highest likelihood of a defect (4.17 per 10,000 births); for non-Hispanics the risk is 3.22 per 10,000 births and for African-Americans the risk is lowest at 2.64 per 10,000 births [12]. There are geographic and temporal variations in incidence as well [13, 14].

Women with low folic acid levels and/or impaired folate-mediated pathways or antibodies to folate are known to be at increased risk of NTDs [15]. Folic acid supplementation in prospective, randomized trials result in a 50–70% decrease in NTDs (Vitamins to prevent neural tube defects, 1991; [15, 16]). In 1992 the U.S. Public Health Service recommended women of childbearing age take a folic acid supplement (400 μg) daily, even before they become pregnant (Recommendations for the use of folic acid, 1992) because the neural tube develops early in gestation, prior to women realizing they are pregnant [15–17]. However, only 1/3 of women took folic acid supplements [18], so the government regulated fortification of flour and pasta with folic acid in the late 1990s [19]. These measures have resulted in a 20–50% drop in prevalence of NTDs [18, 20].

64.2 Risk Factors for the Development of Neural Tube Defects

Familial risk for NTDs is strong; a mother with one affected child has a 20–50 times risk of having another child with an NTD, and for a person with myelodysplasia the risk increases 40 times [21, 22] (Table 64.1).

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_64

Table 64.1 Spinal level distribution for Myelomeningoceles

Location	Incidence (%)
Cervical- high thoracic	2
Lowe thoracic	5
Lumbar	26
Lumbosacral	47
Sacral	20

Other maternal risk factors include: young and advanced age [23]; obesity [24]; diabetes [25]; fever or flu [26]; caffeine consumption [27]; certain occupational exposures [28]; low educational level and socioeconomic status [28]; passive smoking [29]; periconceptual stressful event [30]; low weight gain [31]; use of folic acid antagonists such as valproic acid and/or carbamazepine [32, 33]; preceding history of miscarriage [34] or other birth defect [34]; and higher birth order [35].

64.3 Pathogenesis

Almost all infants born with MMC have an Arnold-Chiari malformation—hindbrain herniation, brainstem abnormalities, low-lying venous sinuses, and a small posterior fossa [36]. This produces hydrocephalus and developmental brain abnormalities [36] that affects motor, cranial nerve, and cognitive functioning. Hydrocephalus has been managed by shunting cerebral spinal fluid to the peritoneal cavity [36] but endoscopic third ventriculostomy combined with choroid plexus cauterization has come into vogue, avoiding the need for ventriculoperitoneal (VP) shunting in 70%, with similar neurocognitive outcomes as those with a VP shunt [37, 38].

The neurologic lesion produced by the myelomeningocele can be variable, depending on what neural elements, if any, have everted with the meningocele sac. The bony vertebral level often provides little or no clue to the exact neurologic level or lesion produced. The height of the bony level may differ from the highest extent of the neurologic lesion from one to three vertebrae in either direction [39]. The neurologic lesion produced has a variable influence on LUT function that cannot be predicted just by observing the spinal abnormality or the neurologic function of the lower extremities.

64.4 Perinatal Concerns

Antenatal ultrasonography has shown the insult to the central and peripheral nervous systems is progressive, with loss of lower limb movement, hindbrain herniation and worsening hydrocephalus during gestation [40]. Animal studies demonstrate covering SB-like lesions prenatally can preserve neurologic function and limit hindbrain herniation [41]. Thus, the neurologic deficit in SB results from two "hits": (1) initial failure of neural tube formation and (2) ongoing injury of exposed neural tissue in the intrauterine environment resulting from mechanical and chemical trauma [36, 41]. Therefore, it was postulated in utero intervention might improve outcomes for children with SB.

Consequently, a randomized trial of prenatal surgery before 26 weeks of gestation versus standard postnatal repair of myelomeningocele was begun—the Management of Myelomeningocele Study (MOMS). Its primary outcome—the need for cerebrospinal fluid shunting—was reduced in the prenatal surgery group (relative risk of 0.70). However, 40% of the prenatal closure group still required shunting, and not all experienced improved neuromotor function or complete resolution of hindbrain herniation. The second primary outcome—a composite score of mental development and motor function at 30 months—was better in the prenatally treated group. Fetal and neonatal deaths did not differ between the two groups and no maternal deaths occurred. But, pregnancy complications, (oligohydramnios, chorioamniotic separation, placental abruption, need for transfusion at delivery and spontaneous membrane rupture) were more common in the prenatal group. A third of mothers with prenatal surgery had uterine dehiscence or a very thin surgical scar at time of delivery. Those fetuses undergoing prenatal surgery were likely to be preterm – 34.1 weeks (13% delivered before 30 weeks) compared with 37.3 weeks of gestation in the postnatal surgery group (none delivered before 30 weeks). Finally, the prenatal surgery infants had more procedures for delayed spinal cord tethering and a higher rate of respiratory distress syndrome and a lower birth weight [36].

64.5 Bladder Function After Prenatal Closure of Mylemeningocele

Several studies involving small number of children having had in utero closure had urodynamic parameters similar to those for children undergoing postnatal repair [42, 43]. One study revealed prenatal closure results in a higher incidence of complete denervation of the external urinary sphincter and detrusor overactivity compared with a postnatal closure group [44]. Studies involving larger numbers of prenatally closed infants with those closed postnatally confirmed there was no difference in the need for CIC, bladder capacity, detrusor overactivity [45–47], incontinence between catheterizations, antimuscarinic use, antibiotic use, detrusor-sphincter dyssynergia (DSD) [46], incidence of detrusor leak point pressure exceeding 40 cm H_2O, vesicoureteral reflux (VUR), need for a bowel regimen, or need for augmentation cystoplasty, a Mitrofanoff catheterizable channel, or a Malone antegrade continence procedure [45].

Thus, prenatal closure of MMC seems to improve neuromotor function and decreases the need for ventriculoperitoneal shunting but this advantage comes at the risk of maternal morbidity and preterm labor. Also, it is clear bowel and bladder function are not improved and may be hindered by prenatal surgery when compared with postnatal closure.

64.6 Initial Postnatal Management

Performing urodynamic testing immediately after birth is ideal, but the risk of spinal infection and the need for prompt closure has not made this a viable option. Only one study achieved this, with 3.3% (1 in 30) experiencing a change in neurologic status following spinal canal closure [48]. Therefore, urodynamic studies are delayed for a short period of time after birth (<3 months). However, residual urine is measured by ultrasound or catheterization after the child voids or leaks urine with a Valsalva maneuver early in the postoperative period [49, 50] and CIC begun if the volume is >5 mL, as normal bladder capacity in the newborn period is 10–15 mL. Other tests include urinalysis and culture, serum creatinine determination (after the first week of life, as it reflects maternal levels before that) [49], and a careful neurologic examination of the lower extremities.

Renal ultrasonography is performed to assess upper urinary tract architecture and function once the spinal closure has healed sufficiently. Hydronephrosis, ureteral dilation, renal size or contour discrepancy, or increased bladder wall thickness warrant voiding cystourethrography (VCUG) [49, 50]. Abnormal urodynamic (UDS) parameters (detrusor overactivity, poor compliance, elevated leak point pressure, or DSD) also merit a VCUG [49, 50]. The UDS satisfy several objectives by providing: baseline information explaining the radiologic appearance of the upper and lower urinary tract as well as the status of the sacral spinal cord and the central nervous system (CNS); information that can be compared with findings on subsequent assessments, so early signs of deterioration of urinary tract function and drainage, or progressive neurologic denervation, can be detected; infants at risk for urinary tract deterioration resulting from a poorly compliant or overactive detrusor or outflow obstruction from DSD, which determines the need to initiate prophylactic measures before any deterioration in upper urinary tract architecture and function actually takes place, to be identified; and information to counsel parents about their child's future bladder and sexual function [51–56]. A dimercaptosuccinic acid (DMSA) renal scan is recommended when hydronephrosis or vesicoureteral reflux is present from a hostile bladder environment as detected on UDS.

64.7 Findings

Five percent to 10% of newborns have an abnormal urinary tract on their first radiologic examination; 3% have hydroureteronephrosis secondary to spinal shock, from the spinal canal closure [57], and 15% have abnormalities that developed *in utero* as a result of abnormal LUT function from outlet obstruction [58].

UDS in the newborn period have shown 63% have bladder contractions irrespective of the level of the lesion – 50% of infants with upper lumbar or thoracic lesions and sacral spinal cord sparing, have detrusor overactivity. Thirty-seven percent have an acontractile detrusor with detrusor compliance that is either good (20%) or poor (17%) [52–54, 58]. Electromyography of the external urethral sphincter demonstrates an intact sacral reflex arc with no lower motor neuron denervation in 40%; partial denervation in 24%; and complete loss of sacral cord function in 36% [58].

64.7.1 Prediction of Risk of Upper Urinary Tract Deterioration

Combining bladder contractility and external sphincter activity leads to three categories of LUT dynamics: synergy (26%), dyssynergy (DSD) with and without poor detrusor compliance (37%), and complete denervation (36%) [55, 58] (Fig. 64.1). DSD occurs when the external sphincter fails to decrease or actually increases its activity during a detrusor contraction or a sustained increase in intravesical pressure as the bladder is filled to capacity [59]. Frequently, a poorly compliant bladder with high intravesical pressure occurs in conjunction with a dyssynergic sphincter, resulting in a bladder that empties only at high intravesical pressure [55].

Synergy is characterized by complete silencing of the sphincter during a detrusor contraction or when bladder capacity is reached at the end of filling. Voiding pressures are usually normal. Complete denervation denotes no bioelectric potentials in the external sphincter at any time during the micturition cycle or in response to sacral stimulation or a Credé maneuver.

Categorizing LUT function like this has proved useful because it reveals which children are at risk for urinary tract changes, which should be treated prophylactically, or alternatively, need close surveillance. Within the first 3 years of life, 71% of newborns with DSD had urinary tract deterioration on initial assessment or subsequently, whereas only 17% of synergic children and 23% of completely denervated individuals developed similar changes. Infants in the synergic group who showed deterioration did so only after they converted to a dyssynergic sphincter function. Among the infants with complete denervation, those who showed deterioration

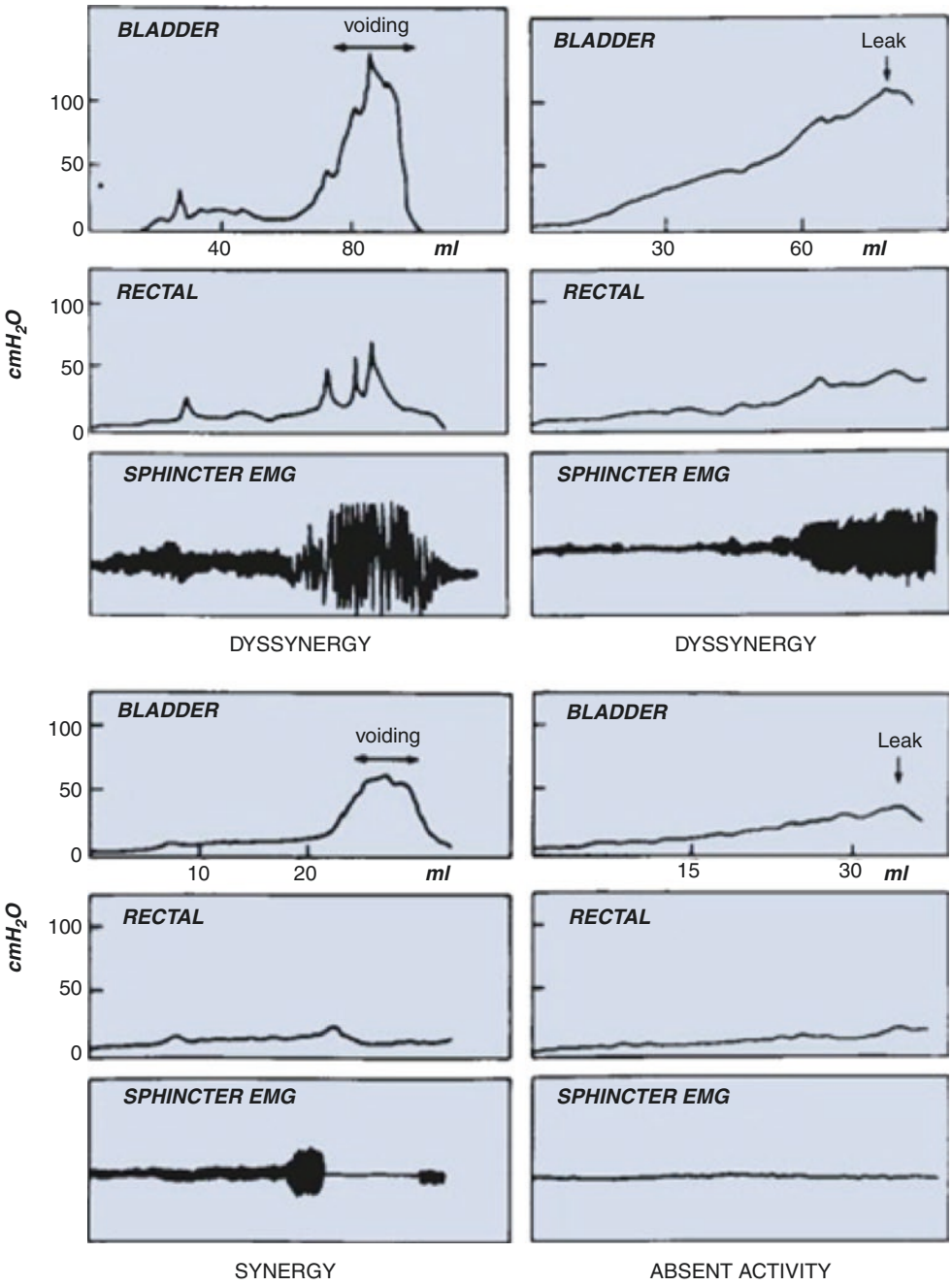

Fig. 64.1 Schematic of the types of urodynamic findings (combining both cystometrogram tracing and sphincter EMG activity) in babies with myelodysplasia. Note dyssynergy has two forms: an active increase in sphincter EMG activity with a bladder contraction AND a non-relaxing sphincter when capacity is reached at the end of the cystometrogram. Synergy implies spontaneous cessation of EMG activity when the bladder has a contraction at capacity, and absent activity reveals no electrical activity in the sphincter muscle as the bladder fills to capacity

had increased levels of urethral resistance, presumably caused by fibrosis of the skeletal muscle component of the external sphincter. Thus, it seems bladder outlet obstruction is the major contributor to the development of urinary tract deterioration in these infants. Poor detrusor compliance plays an important role, especially when outlet resistance exceeds 40 cm H_2O [51, 60, 61]. Detrusor compliance appears to worsen in children with high levels of outlet resistance [62].

Detrusor filling pressures were looked at more critically to determine whether they are an important factor in upper urinary tract deterioration. Landau and colleagues developed the concept of low detrusor filling pressure (less than 30 cm H_2O) at specific volumes adjusted for age, and not at maximal capacity [60] as being important. Applying this concept, they detected significantly improved sensitivity in predicting upper urinary tract deterioration.

64.8 Early Intervention in Children with Myelodysplasia

Early intervention, defined as CIC and antimuscarinic therapy, for children with DSD, poor compliance, high bladder pressures, and out flow obstruction was introduced in the early 1990s [51, 54, 55]. Controversy regarding the benefits of early intervention in children with myelodysplasia still exist but an ever increasing plethora of data documenting its salubrious effect on outcomes abound.

64.8.1 Effect of Early Intervention on Bladder Function

One study of 26 newborns with DSD and high bladder pressures treated with CIC and oxybutynin, revealed overactive contractions were eliminated in two with this overactivity and lower peak contractile pressure were achieved in the remaining 12, while lower detrusor filling pressure at capacity occurred in all 12 patients with poor compliance [63]. Minimal side effects were noted [63] and early intervention resulted in improved continence [64] with 44% of children being dry at age 6 years with no other therapy (Fig. 64.2) [65].

64.8.2 Early Initiation of Clean Intermittent Catheterization Decreases the Rate of Urinary Tract Infection

Studies of expectant management document urinary tract infection (UTI) in 50% of children by 15 months of age and 81% by the age of 15 years, with recurrent UTIs common; over 44% having five episodes and almost 10% with >20 episodes of UTI [66], whereas in children treated early with CIC, the mean number of infections is 0.3 per year [67]. Other studies have demonstrated a decreased

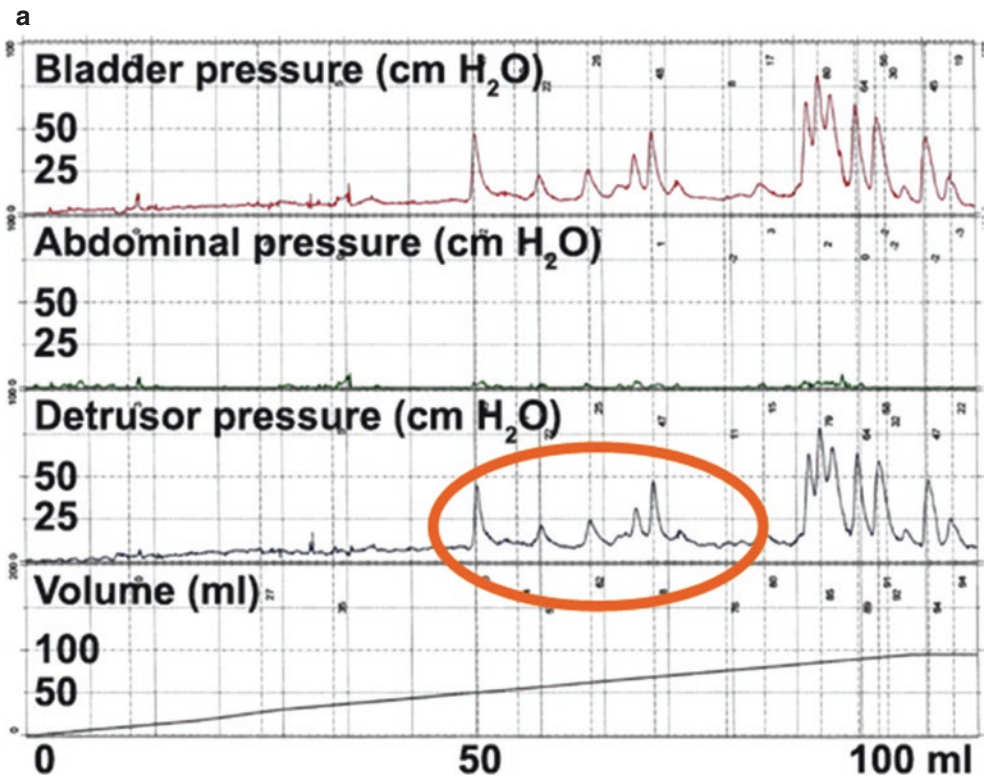

Fig. 64.2 (**a**) The cystometrogram reveals detrusor overactivity during filling. (**b**) The cystometrogram demonstrates resolution of overactivity in response to anticholinergic medication. (**c**) The cystometrogram denotes a poorly compliant bladder during filling. (**d**) The cystometrogram shows marked improvement in bladder compliance with minimal rise in pressure after anticholinergic medication has been administered

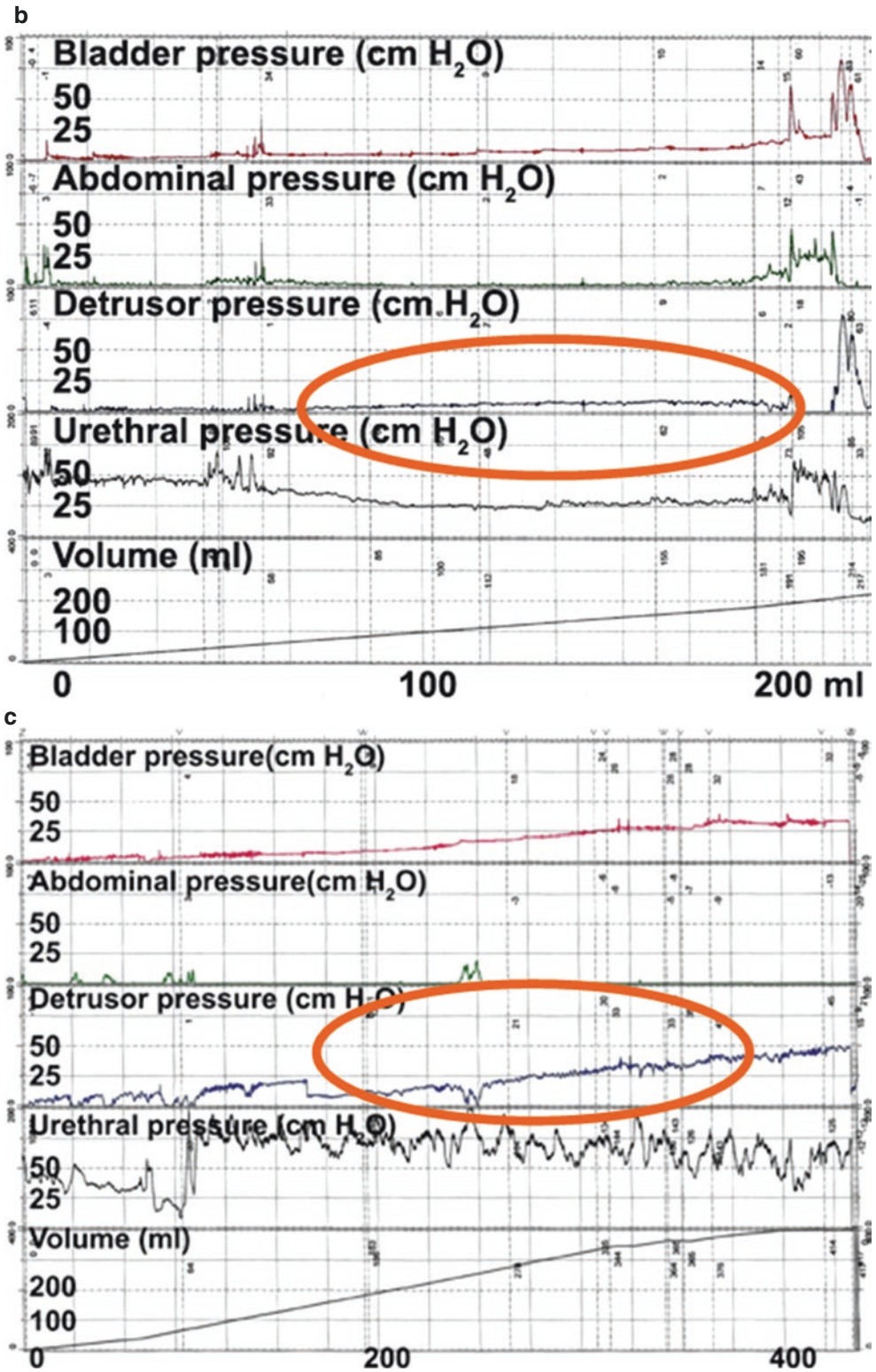

Fig. 64.2 (continued)

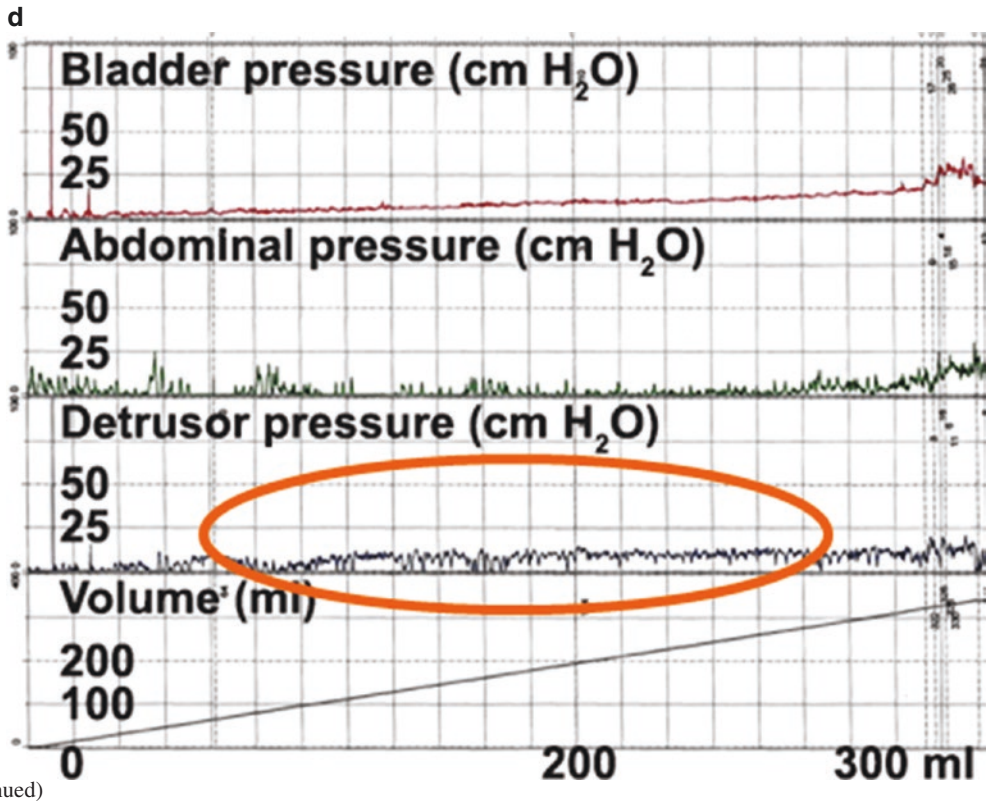

Fig. 64.2 (continued)

rate of UTI in children on CIC, either involving the same patient [68] or contrasting a comparative group [69].

64.8.3 Early Intervention Decreases Upper Urinary Tract Deterioration

The potential for developing hydroureteronephrosis in children with high-risk bladders (presence of DSD) is well established; 72% of children with DSD developed hydronephrosis [54]. Others noted hydroureteronephrosis in children with high-risk bladders treated expectantly varied from 18 to 80% [64, 70–72]. Hydrouteronephrosis is much less common in children treated early—range, 0–15% [64, 65, 70].

64.8.4 Early Intervention Reduces Rate of Vesicoureteral Reflux

Studies of expectant management of children with high-risk bladders identify VUR in up to 50% by 9 years of age [66]. When CIC is begun at birth, VUR development is much less common (28%) [67] or found to be of lower grade compared to those children not on or non-compliant with therapy (62% vs. 92%) [69] (Fig. 64.3).

64.8.5 Early Intervention Decreases the Need for Surgery

Several studies comparing early intervention with expectant therapy noted a lower need for renal protective surgery in children with high-risk bladders—11% in those treated expectantly versus no surgery in 41 children treated early [66]. In fact, only one child in the early treatment group required surgery for incontinence, and six received injection of botulinum toxin [67]. Others have documented an 18–24% reduction in the need for bladder augmentation when early intervention is compared with expectant management [64, 72].

64.8.6 Early Intervention Decreases the Incidence of Renal Scarring and End-Stage Renal Disease

Some investigators found early intervention isn't advantageous for children who empty their bladder spontaneously [73], but historical cohort studies document renal scarring in 27–50% of children [66, 74, 75]. The rate of scarring in children treated early is much lower, ranging from 4 to 12% [65, 67, 73] and a decreased incidence of end stage renal disease (ESRD) (0–1.6%) [65, 73, 76] versus 30%, when compared with those managed expectantly [77] (Fig. 64.4).

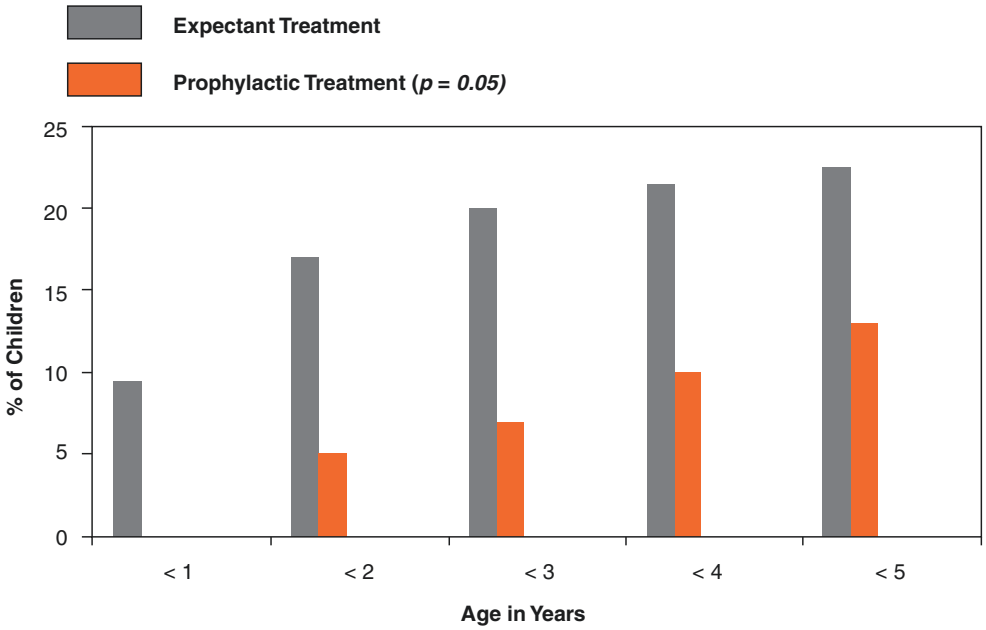

Fig. 64.3 The incidence of reflux is dramatically reduced in all ages during the first 5 years of life in children with myelodysplasia who were prophylactically treated, when compared with those who were treated expectantly

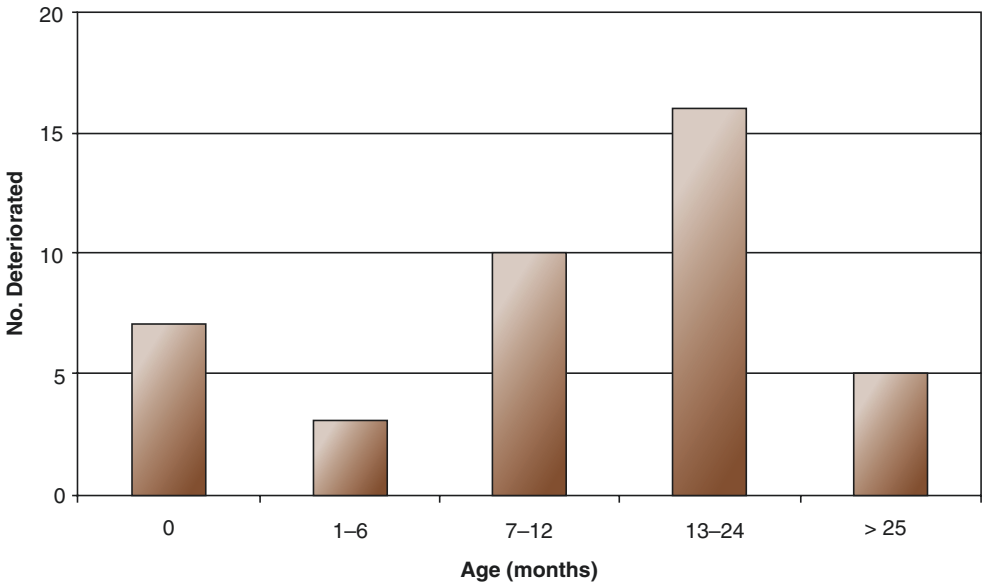

Fig. 64.4 The incidence of deterioration (hydronephrosis and/or vesicoureteral reflux) involving the upper urinary tract in those children with myelodysplasia, treated expectantly. Note the substantial incidence of deterioration in children less than 2 years of age

64.9 Assessment of Renal Function in Children with Neuromuscular Dysfunction of the Lower Urinary Tract

Serum creatinine is a poor but widely used marker of glomerular filtration rate (GFR), especially in children with neurogenic bladder dysfunction. Creatinine produced from the nonenzymatic degradation of creatine from muscle is freely filtered and secreted by the kidney [78]. Its serum level is dependent on age, gender, height, and muscle mass [79]. Individuals with reduced muscle mass often demonstrate a low endogenous creatine release that doesn't result in elevated creatinine levels despite a decrease in GFR [80]; thus, serum creatinine is not an accurate reflection of GFR in myelodysplastic children, who often have deficient muscle mass [79–81]. Currently, the gold standard for measuring GFR is the DMSA renal scan, which is invasive and has a high radiation exposure but preferable to a serum marker that does not closely reflect GFR in this population at high risk for renal impairment.

Small molecular weight proteins, e.g., cystatin C, have been suggested as alternative markers of GFR in this population [79]. Cystatin C is a 13-kDa cysteine proteinase inhibitor, produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus, not secreted from the renal tubule, and almost entirely catabolized in the proximal

tubule [82]. Thus, serum concentration of cystatin C is determined strictly by glomerular filtration. When compared with other standards for measuring GFR in SB children, serum cystatin C levels correlate more closely with GFR than that estimated by the Schwarz formula or other low-molecular-weight proteins [79, 83]. However, cystatin C may not be a reliable marker in early stage renal impairment [81, 83]. A formula for estimating GFR from serum creatinine in children has been proposed, log(GFR) = 1.962 + [1.123*log(1/CysC)] [81]. A recent meta-analysis in a diverse population of adults revealed cystatin C more accurately predicts the risk of ESRD and death than creatinine [84]. Thus, cystatin C is superior to serum creatinine for estimating GFR; however, when mild renal functional impairment is suspected, a full nuclear medicine clearance study may be required.

64.9.1 Kidney Size in Children with Spina Bifida

Sutherland noted children with SB had smaller kidneys than their normal peers and generated a nomogram for renal size in this population [85]. This finding has been confirmed [86, 87]. A potential cause could be low levels of growth hormone, but this has been excluded by demonstrating normal levels of insulin-like growth factor-1 [86, 87]. One study of newborns with SB found those with small kidneys, and their mothers, had high serum levels of homocysteine but also had a higher incidence of intrauterine growth retardation. As hyperhomocysteinemia has been linked to placental vasculopathy, the mechanism for small renal size in SB children might be related to abnormal placental function [87]. Small renal size in children with SB has also been associated with decreased renal function [86].

64.9.2 Renal Dysfunction in Myelodysplasia

Surrogate markers of renal function in children with SB are frequently abnormal; 54% and 19% of children referred to nephrologists for recurrent UTI were noted to have microalbuminuria and metabolic acidosis, respectively [68]. The rate of hypertension in myelodysplastic children ranges from 12 to 41% [68, 77, 88], which is significantly higher than the 3% noted in national age-matched normal controls [88]. The risk of hypertension is positively correlated with maximum body mass index [88] and frequently noted after puberty and in those with renal scarring [77].

Varying degrees of renal dysfunction has been noted in 30–50% of children with SB [75, 76]. End stage renal disease (ESRD) is noted in 18% of children before and 30% after puberty [77]. Others found ESRD in 15% of those with SB (Cy, 2010). Early intervention with CIC and antimuscarinics lowers the rate of renal dysfunction (6%) and ESRD (0–1.6%) [65, 73, 76].

64.9.3 Determinants of Risk of Renal Dysfunction in Myelodysplasia

The cause of renal functional loss in children (defined as altered renal function, measured by creatinine or creatinine clearance or renal scarring noted on DMSA renal scans) has been associated with hydronephrosis [73], VUR [54, 74, 89–91], high detrusor pressures [67, 89, 91], detrusor overactivity [91] and febrile UTI [91, 92]. However, a multivariate analysis demonstrated high detrusor pressure and hydronephrosis, in the absence of VUR, was not associated with renal cortical loss [90]. Lack of compliance with recommended therapy has also been shown to be important in the development of renal scarring [67, 69].

64.10 Sexual Function

Sexual function is becoming an increasingly important issue as more individuals reach adulthood and want to marry or to have intimate relationships [93]. Psychosocial factors play a major role in development and sexual maturation in SB children just as they do in normal children, but parents and health care workers are reluctant to discuss sexual matters with their children [94–96]. Teens with SB often experience social isolation [95, 97]. This is supported by studies showing they are less likely than those without MMC to have peers acting as the main source of their sexual education [95, 98]. Some with MMC are dependent on caregivers for activities of daily living; therefore, they live with parents longer or with alternative caregivers [99]. Young men with MMC reported better erectile function and intercourse satisfaction when living independently [100]. When asked about sexual function, many teens with MMC report parents are overprotective and less willing to grant autonomy for adequate peer and sexual development [97, 101]. Parental permissiveness in social participation and age-appropriate treatment by parents contribute positively to high self-esteem in these adolescents [102]. Regarding satisfaction levels, in a study of Dutch young adults with SB, the highest proportion of dissatisfaction was found for partnership relations (49%) and sex life (55%). More than 50% of young adults with SB report they are dissatisfied with their current sex life [103]. Males were much more dissatisfied with their sex life than females [104].

Boys reach puberty at an age similar to that for normal males, whereas breast development and menarche tend to begin as much as 2 years earlier than usual in myelodysplastic females (compared with normal girls). In 15% of girls

with SB, the average age at menarche varies from 10.9 to 11.4 years [105]. The cause of this early hormonal surge is uncertain, but may be related to changes in pituitary function secondary to hydrocephalus [106].

Sexual education specific to individuals with SB include using latex-free condoms for those with latex allergy or those adhering to latex avoidance recommendations, and warning females that estrogen and progestin contraceptives may increase the risk of thromboembolic events in those with decreased mobility, while intrauterine devices for contraception is unsafe owing to potential pelvic infections [107].

Several axioms have evolved following research into sexual function in myelodysplastic patients: the degree of sexuality is inversely proportional to the level of neurologic dysfunction [95, 108, 109]; less sexual indulgence occurs in those with greater degrees of incontinence and more severe disability [94, 99, 103, 109, 110]; those with sacral level lesions are most likely to form partnerships [109]; increasing age is associated with a greater chance of having a partner (those over 26 years were 2.1 times more likely to have a partner than those aged 18–25 years [109]; the absence of hydrocephalus is a positive predictor of sexual activity [103], more so for women than men [110]; females are more likely than males to be sexually active [103, 110, 111] but are at greater risk for sexual abuse, with 37% noting unwanted sexual attention and 30% unwanted sexual touching [111] while 4% of men experiencing improper sexual touching [111].

Interviewing teenagers with MMC has shown 28–40% have had one or more sexual encounters with almost all having the desire to marry and ultimately to bear children [93, 108]. Seventy percentage desire sexual contact [103]. Common limitations when evaluating sexual function in adolescents and young adults is their low participation rates because patient or parental refusal and the elimination of patients with severe physical disabilities and/or severely compromised intellectual function. The result is a selection bias, in which only highly functioning individuals are studied. Five of six studies found >70% of young men were able to attain an erection (range 70–92%) [94, 98, 99, 112, 113]. The ability to ejaculate was noted to range from approximately 40–75% [94, 98, 99, 112], but some had retrograde ejaculation [94]. Self-reporting of sexual activity varied greatly ranging from 8 to 83% for males [94, 98, 99, 112, 114] and 23 to 69% for females [99, 112].

Pregnancy and an uneventful delivery were achievable in 70–80% of women, although urinary incontinence in the latter stages of gestation was common in many, as was delivery by cesarean section [7, 112, 114, 115]. Among males, 17–39% claimed that they were able to father children, and another 25% had a good prognosis for fathering them [7, 98, 114]. As noted earlier, both men and women with SB have an increased risk of having a similarly affected child, compared with normal individuals (3.7% incidence of SB in offspring) [116]. This effect is more pronounced in females [117]. If both parents have SB, the risk of having an affected child approaches 15% [118]. To reduce this risk, menstruating women with SB should be counseled about taking 4.0–5.0 mg of folic acid supplement daily before contemplating getting pregnant [20].

It is more likely that men will have problems with erectile and ejaculatory function because the sacral spinal cord is frequently involved, whereas reproductive function in women, which is under hormonal control, is not affected. Men with neurologic lesions at S1 or lower are likely to have normal or adequate reproductive sexual function, but only 50% of those with lesions above that level have adequate function [120, 121]. Poor semen quality [122] and Sertoli cell–only histology on testis biopsy [123] have been reported as reasons (in addition to erectile dysfunction) for infertility in these men.

The International Index of Erectile Function (IIEF) a validated questionnaire to evaluate sexual function in men older than 18 years found 75% had erectile dysfunction [100]. Of the 16 men who recently had sexual intercourse, 4 had no erectile dysfunction, 3 had mild dysfunction, 4 had mild-to-moderate dysfunction, and 5 had severe dysfunction. Erectile function was directly related to the ability to maintain an erection and the presence of a sacral nerve root lesion [100]; an intact pelvic parasympathetic reflex had a positive correlation in these men [94, 113].

Medical therapy for erectile dysfunction has been effective. Sildenafil improved erectile function in 80% in a randomized, double-blinded, placebo-controlled trial [108]. Some promise has been shown when attempting to restore penile sensation by connecting the sensory ilioinguinal nerve microsurgically to the ipsilateral dorsal nerve of the penis in men with normal groin sensation [124, 125]. Small case series showed increased sensation of the ipsilateral glans penis, better overall sexual function, and increased satisfaction [125] but these findings await long-term analysis.

64.11 Management of Neurogenic Bowel Dysfunction in Myelomeningocele

Options for the management of constipation traditionally include dietary modification, digital stimulation, laxatives, enemas, and biofeedback therapy. Management in children with neurogenic bowel must to be tailored to the individual's ability to address mobility and balance, ability for self-care, manual dexterity, and anal sphincter tone.

Two thirds of children aged 6 and older and one third of children and young adults aged 16–25 years with SB, report fecal incontinence. This has a substantial impact on their quality of life [126, 127]. Therefore, a graduated approach to the management of constipation is recommended [128–131]. Initially, treatment is directed toward high dietary fiber and osmotic laxatives [128, 131]. Polyethylene glycol has been

shown to be more effective than lactulose [132]. An option for those who are unable to sit on the toilet is controlled constipation with manual evacuation of stool because large-volume enemas cannot easily be delivered in these children [128]. In those who are able sit independently, with some anal sphincter activity, a regular postprandial toilet sitting regimen three times daily after meals has been effective, as it employs the gastrocolic reflex to initiate a bowel movement [128]. When continence is not achieved by defecation, digital stimulation is suggested [128]. If manual evacuation fails or if the anal sphincter is nonfunctioning, retrograde enemas (tap water with irrigation cone) followed by kneading of the abdomen or alternative transanal irrigation devices [133] are instituted [128, 134]. Initially enemas are given daily, and if successful, the frequency can be decreased to every second day or so, depending on how long the individual remains continent of feces. Initial enema volume is 500 mL and increased to one liter, if required. The Peristeen enema technique has been effective in many who otherwise are unable to have a controlled enema instillation.

If fecal incontinence persists beyond this point, the antegrade continence enema (ACE) is considered the next step. This is achievable through a Mickey button or employing the appendix or small segment of bowel refashioned to create a continent catheterizable channel. Once matured, an antegrade continent enema is begun daily but reduced to 4–5 times per week as needed over time. Instillation volumes range from 1 to 2 L [128]. This stepwise approach to fecal pseudocontinence is successful in 69%; 10% achieve fecal continence. Of those who are pseudocontinent, 16% use manual evacuation, 10% a toileting scheme, 42% a retrograde enema, and 32% an ACE [128]. The addition of polyethylene glycol (GoLYTELY), mineral oil, polyethylene glycol 3350 (MiraLAX), or glycerin added to tap water solutions has successfully increased the continence rate for ACE regimens [135].

An ACE delivered through a surgically created appendicostomy was described in children with SB or anorectal malformations by Malone while a percutaneous cecostomy under fluoroscopic guidance was described by Shandling and colleagues, in 1996, the latter has the advantage of avoiding laparotomy or laparoscopy [136]. The ACE has been shown to significantly improve fecal continence, not increase the amount of time dedicated to bowel care, and improve quality of life [137]. Anal plugs may be effective for some during specific activities, e.g., swimming [128]. Long-term studies indicate approximately 40% discontinue using their surgically created cecostomy after a median of 11 years. Reasons for nonuse include lack of effectiveness, complications, psychologic issues, and poor compliance [138]. In those who continue the cecostomy approach, satisfaction levels are very high [138].

64.12 Initial Diagnostic Evaluation and Follow-Up of Congenital Neuropathic Dysfunction in Children

The initial diagnostic evaluation of neuropathic bladder dysfunction as it relates to specific pathologic processes has been discussed throughout the chapter. The International Children's Continence Society (ICCS) has published general recommendations for the follow-up of congenital neuropathic bladder that are a compilation of best practices as a result of a paucity of high-level evidence [49]. These recommendations are based on developmental stages and associ-

Table 64.2 Recommendations from the International Children's Continence Society for evaluation and follow-up of congenital neuropathic bladder and bowel dysfunction in children

Age group	Type of investigation	Recommended frequency of testing	Indication for investigation
Newborn—toddler	Ultrasound	Every 6 months till age 2 years	↑ Risk of tethering due to rapid growth
	Urodynamic studies	Every 12 months	UTIs or lower extremity changes
	DMSA scan	When indicated	If VUR on first VCUG/RNC or febrile UTIs
Toddler—adolescent	Ultrasound	Every 12–24 months	↓ Risk of tethering with slower growth; may ↓ as velocity is reduced
	Urodynamic studies	When indicated	Changes in continence, hydronephrosis, ambulation or lower extremity function
	VCUG/RNC	When indicated or yearly	Recurrent UTI
	DMSA scan	When indicated	Febrile UTIs
Adolescent—adult	Ultrasound	Every 12–24 months	↓ Risk of tethering with slower growth; may ↓ to every 24 months once velocity has reduced
	Urodynamic studies	When indicated	Changes in continence, new or Δ in hydronephrosis, recurrent UTIs
	VCUG/RNC	When indicated	Recurrent UTI
Adult	Ultrasound	Every 18–24 months	↓ Risk of tethering without ongoing somatic growth
	Urodynamic studies	When indicated	Changes in continence, new or Δ in hydronephrosis, recurrent UTIs

ated growth spurts in the first 2 years of life and throughout adolescence when there may be an increased risk of spinal cord tethering (Table 64.2). A recent review of adults followed at a multidisciplinary SB clinic revealed affected individuals developed a urologic issue at a median of 12 months with 40% having an asymptomatic urologic issue at 36 months. This suggests a follow-up period of 12–18 months in adulthood is prudent [139].

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Multiple System Atrophy

65

Ryuji Sakakibara

65.1 Introduction

Multiple system atrophy (MSA) is an uncommon but well-recognized disease entity that both neurologists and urologists may encounter. The term MSA was introduced by Graham and Oppenheimer in 1969 to describe a disorder of unknown cause affecting extrapyramidal, cerebellar, and autonomic pathways [1] MSA includes the disorders previously called striatonigraldegeneration (SND) [2], sporadic olivopontocerebellar atrophy (OPCA) [3], and Shy–Drager syndrome [4]. The discovery in 1989 of glial cytoplasmic inclusions in the brains of patients with MSA [5] provided a pathological marker for the disorder (akin to Lewy bodies in idiopathic Parkinson's disease (IPD)) and confirmed that SND, OPCA, and Shy–Drager syndrome are the same disease with differing clinical presentations. Immunocytochemistry showed that the glial cytoplasmic inclusions of MSA are ubiquitin-, tau-, and alpha-synuclein (SNCA)-positive, possibly representing a cytoskeletal alteration in glial cells that results in neuronal degeneration [6, 7]. SNCA is a presynaptic neuronal protein encoded by the SNCA gene located on chromosome 4. This protein appears to play a role in dopamine and other neurotransmitter metabolism, vesicle trafficking, modification of synaptic transmission, and regulation of membrane permeability. In contrast, pathologically increased expression and abnormal conformation of SNCA are reported to reduce neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis [6, 7] Familial occurrence is estimated to account for 1.6% of all cases, and data on such cases are being accumulated to identify candidate genes for this disorder, including SNCA, MAPT (microtubule-associated protein tau), etc.

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Autonomic failure (postural hypotension and urinary dysfunction) is fundamental to the diagnosis of MSA: it is diagnosed when the criteria of either postural hypotension (systolic blood pressure fall >30 mmHg or diastolic >15 mmHg) or urinary dysfunction (persistent, involuntary urinary incontinence/incomplete bladder emptying) or both are fulfilled, along with poorly levodopa-responsive parkinsonism or cerebellar dysfunction are fulfilled [8]. Based on the major motor deficits MSA can be classified as MSA-P (parkinsonism-predominant) or MSA-C (cerebellar-predominant) [1]. Clinical differential diagnosis between MSA-P, the most common clinical form, and IPD is difficult even for specialists. However, the lack of one-side dominance and resting tremor, poor response to levodopa, and rapid progression are all red flags indicating MSA. MSA-C can mostly be distinguished from hereditary spinocerebellar ataxias, although some individuals with such disorders do not have apparent heredity. Autonomic failure (AF) is almost invariably present and can be an initial manifestation (AF-MSA) [9]. Autonomic failure occurs in other neurodegenerative diseases, i.e., in a subset of patients with IPD (AF-PD) as well as in pure autonomic failure (PAF), both of which are considered Lewy body diseases. This chapter reviews the current concepts of urinary dysfunction in MSA, with particular reference to urinary symptoms, (video-)urodynamic assessment and sphincter electromyography (EMG), and patient management.

65.2 Urinary Symptoms

Both overactive bladder and large post-void residuals occur in MSA. The second consensus statement on the diagnosis of MSA recognizes that the disease frequently begins with bladder dysfunction (although erectile dysfunction usually precedes that complaint). Patients may present with urinary incontinence, urinary retention, or a combination of incontinence and incomplete bladder emptying [8]. It is impor-

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_65

tant that other common causes of poor bladder control are excluded by a urologist or uro-gynaecologist before the disorder is attributed to the neurological condition [10]. Figure 65.1 show the frequency of troublesome urinary symptoms in 256 patients with MSA compared with 158 aged matched control subjects [11]. Patients with MSA patients had significantly higher prevalence of daytime frequency (45% of women, 43% of men), night time frequency (65%, 69%), urinary urgency (64% of men), urgency incontinence (75%, 66%) than did the controls. Symptom of urinary urgency/ frequency is also referred to as overactive bladder (OAB) [12]. They also had more hesitancy of micturition (62%, 73%), prolonged, poor (71%, 81%), or intermittent stream (61%, 47%), or the need to strain to void (48%, 55%). Of particular importance is that the quality of life (QOL) index in MSA group was significantly higher (i.e. worse) in MSA patients for bladder dysfunction (70%, 76%) than that in controls. Many of them show large post-void residual urine volume >100 mL. Therefore both overactive bladder and large post-void residuals are common in MSA.

Urinary dysfunction precedes postural hypotension. Of various symptoms of AF (erectile dysfunction, urinary dysfunction, postural hypotension, respiratory stridor) in patients

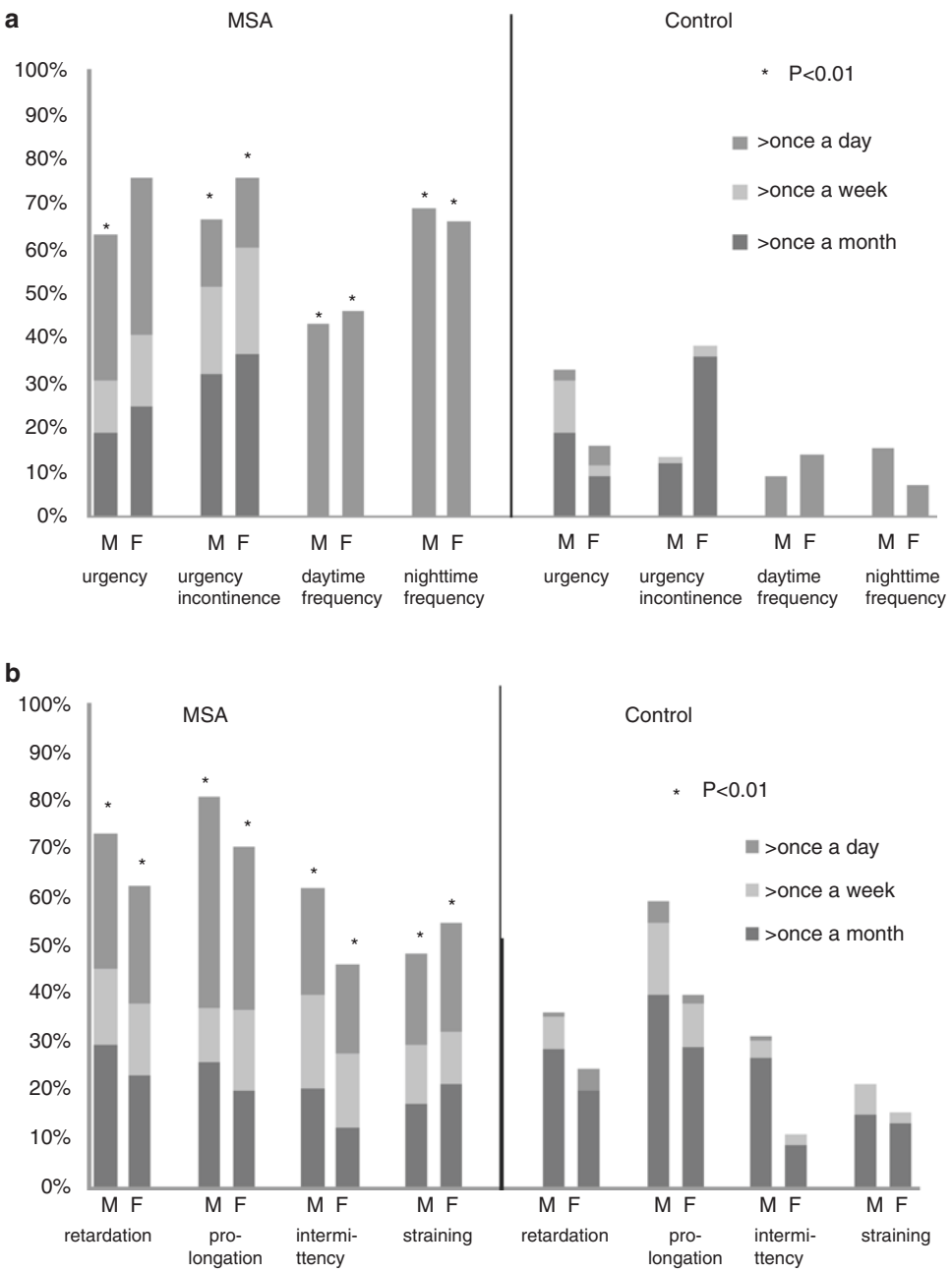

Fig. 65.1 Urinary symptoms in patients with MSA compared to age matched controls estimated by questionnaire. (**a**) Storage symptoms, (**b**) voiding symptoms. Both storage and voiding symptoms in patients with MSA were significantly worse than age matched controls. Particularly they had a significantly higher prevalence of voiding symptoms, particularly retardation in initiating urination (hesitancy) than the controls (cited from [11])

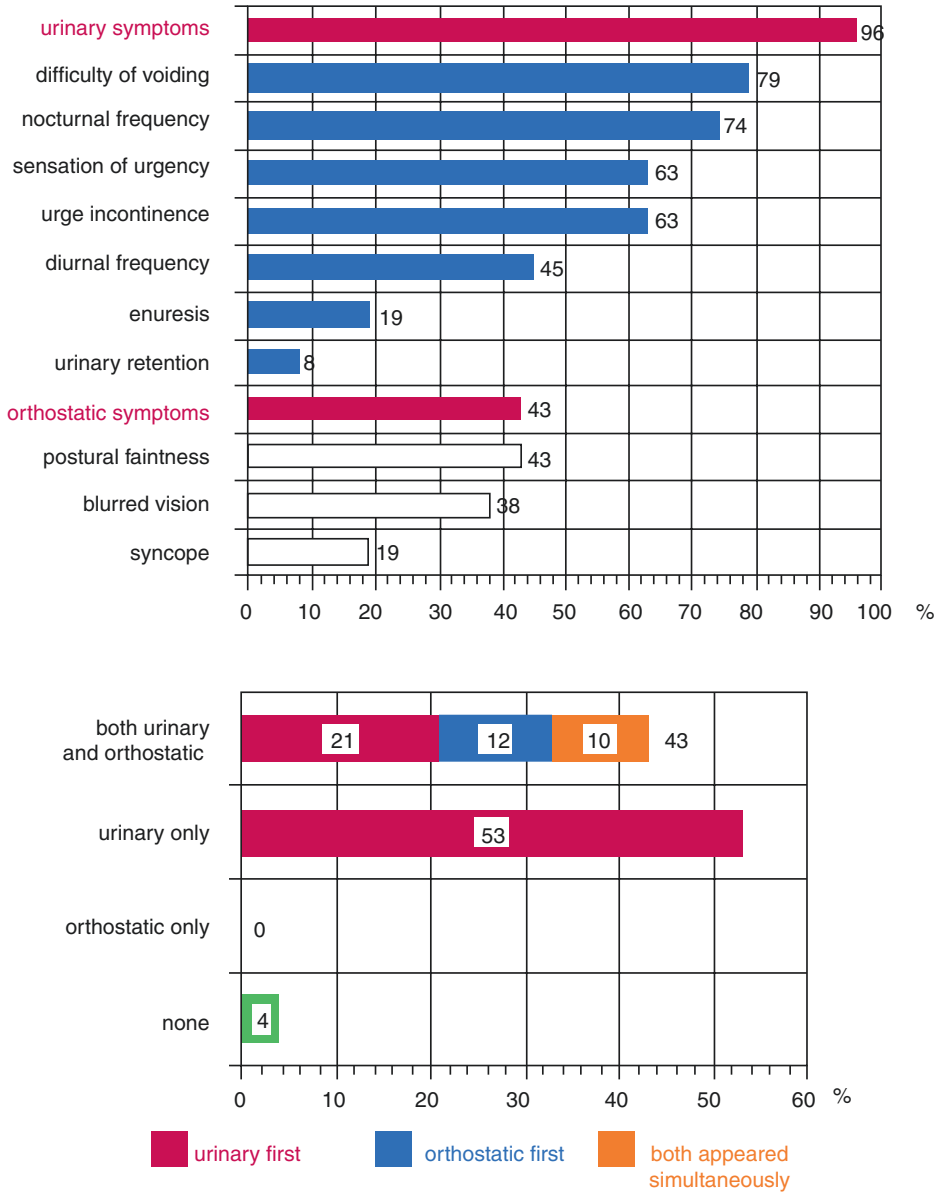

Fig. 65.2 Urinary dysfunction and postural hypotension in MSA (cited from [13])

with MSA, urinary dysfunction has attracted less attention than postural hypotension, although urinary dysfunction may result in recurrent urinary tract infection and cause morbidity. In addition, urinary incontinence results in impaired self-esteem, stress on the caregiver, and considerable financial cost. Postural hypotension was pointed out first in AF-MSA, which turned out to be a marker of autonomic involvement in this disorder. Both of the original 2 patients discussed by Shy and Drager had urinary frequency, incontinence, and urinary retention [4]. Other variants (MSA-P and MSA-C) rarely develop postural hypotension in their early stage. However, in the original reports, 3 of 4 patients with MSA-P showed voiding difficulty, retention, and urinary incontinence [2], and both patients with MSA-C had voiding difficulty and urinary incontinence [3]. Thus, what are the most common and earliest autonomic features of MSA?

In our previous study of 121 patients with MSA [13], urinary symptoms (96%) were more common than orthostatic symptoms (43%) ($p < 0.01$) (Fig. 65.2). The most frequent urinary symptom was difficulty voiding in 79% of the patients, followed by nocturnal urinary frequency in 74%. Other symptoms included sensation of urgency in 63%, urgency incontinence in 63%, diurnal urinary frequency in 45%, nocturnal enuresis in 19%, and urinary retention in 8%. The most frequent orthostatic symptom was postural faintness in 43%, followed by blurred vision in 38% and syncope in 19%. These figures are similar to those of Wenning et al. [14], who noted urinary incontinence in 71%, urinary retention in 27%, postural faintness in 53%, and syncope in 15% of 100 patients with MSA; these figures were recently confirmed by a larger study [15]. In our previous study mentioned above, among 53

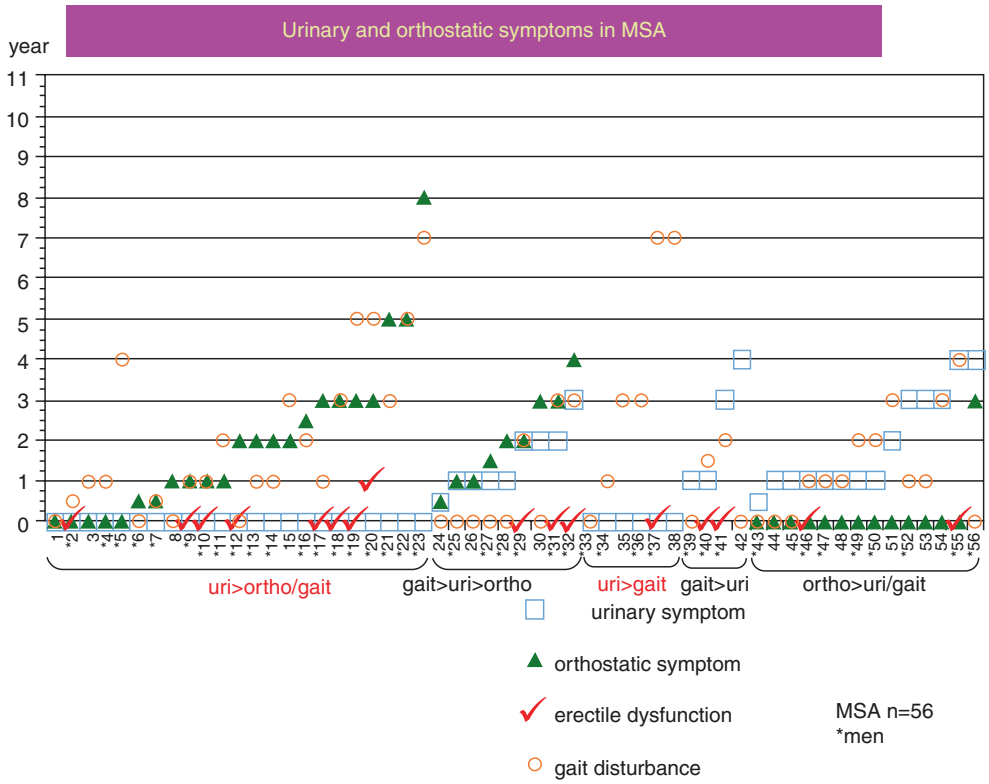

Fig. 65.3 Autonomic and motor disorders in MSA

patients with both urinary and orthostatic symptoms, those who had urinary symptoms first (48%) were more common than those who had orthostatic symptoms first (29%), and some patients developed both symptoms simultaneously (23%) [13].

These findings indicate that urinary dysfunction is a more common and often earlier manifestation than postural hypotension in MSA. Many factors might be involved in this phenomenon. Reports of focal lesions have shown that postural hypotension occurs in lesions below the medulla, whereas urinary dysfunction occurs in lesions at any sites in the neuraxis. MSA lesions involve the pons, the hypothalamus, and the basal ganglia, all of which might affect the lower urinary tract function as described below.

Urinary dysfunction precedes also motor disorder. Looking at both urinary and motor disorders, we see that approximately 60% of patients with MSA develop urinary symptoms either prior to or at the time of presentation with the motor disorder [12, 13] (Fig. 65.3). This indicates that many of these patients seek urological advice early in the course of their disease. Since the severity of urinary symptoms is severe enough for surgical intervention, male patients with MSA may undergo urological surgery for prostatic outflow obstruction before the correct diagnosis has been made. The results of such surgery are often transient or unfavorable because of the progressive nature of this disease. Male erectile dysfunction is often the first presentation [12, 13, 16], possibly preceding the occurrence of urinary dysfunction in MSA. The urologist confronted with a patient showing these features should be cautious about embarking on an operative approach. The neurologist encountering a patient with marked urinary symptoms might consider future investigation by brain magnetic resonance imaging (MRI) and sphincter EMG.

Since motor disorders in MSA mostly mimic those in IPD, the urogenital distinction between these two diseases is worth considering, although a number of earlier studies on 'Parkinson's disease and the bladder' might inadvertently include patients with MSA. The prevalence rate of urinary dysfunction in MSA is higher than the 58–71% rate reported in IPD [13, 17–19]; similarly, that of urgency incontinence in MSA is higher than the 33% rate reported in IPD. In addition, urinary dysfunction is never the initial presentation in IPD.

65.3 Videourodynamic and Sphincter Electromyography Assessments

Since MSA is a neurodegenerative disease that affects multiple brain regions, patients with the disease may have a wide range of urodynamic abnormalities that change with progression of the illness. Videourodynamics and sphincter EMG also enable us to assess the lumbosacral cord functions, which help us distinguish MSA from other parkinsonian disorders.

65.3.1 Bladder Overactivity

Filling phase abnormalities included bladder overactivity in 33–100% and uninhibited external sphincter relaxation in 33% of MSA [12, 19–21], figures similar to those reported in IPD [10, 12–16] (Figs. 65.2 and 65.4). Bladder overactivity is urodynamically defined as an involuntary phasic increase in detrusor pressure (naïve bladder pressure—abdominal pressure) >10 cmH_2O during bladder filling, which is commonly associated with decreased bladder volumes at first sensation and bladder capacity. It is bladder overactivity that seems to be the major cause of urgency incontinence in patients with MSA. But when coupled with uninhibited sphincter relaxation, incontinence may worsen (Fig. 65.4) [22].

It is well known that cerebral diseases can lead to a loss of the brain's inhibitory influence on the spino-bulbo-spinal micturition reflex. The information that arises from the lower urinary tract reaches the periaqueductal gray matter (PAG), then goes down to the pontine micturition center (PMC), an area identical or just adjacent to the locus ceruleus, which then activates the descending pathway to the sacral preganglionic neurons innervating the bladder [23]. The basal ganglia are thought to be one of the higher centers for micturition, since lesions of this area lead to bladder overactivity [24–27]. Recent positron emission tomography (PET) studies have shown that the hypothalamus, PAG, midline pons, and cingulate cortex are activated during urinary filling [28, 29]. The central pathology of MSA includes neuronal loss of neuromelanin-containing cells in the locus ceruleus [30, 31] as well as in the nigrostriatal dopaminergic system ('putaminal slit sign') [6, 27] and cerebellum, and to a lesser extent in the ponto-medullary raphe ('pontine cross sign') [6, 32] and the frontal cortex [33, 34]. Recent experimental studies have suggested that the raphe modulates micturition function [35]. Experimental studies have also suggested that the cerebellum controls micturition function [36]. A single photon emission computed tomography (SPECT) study has shown that in the urinary storage and micturition phases, but not in the resting phase, activation of the cerebellar vermis was significantly lower in MSA patients than in control subjects (Fig. 65.5) [37]. These areas seem to be responsible for the occurrence of bladder overactivity and uninhibited sphincter relaxation in MSA patients.

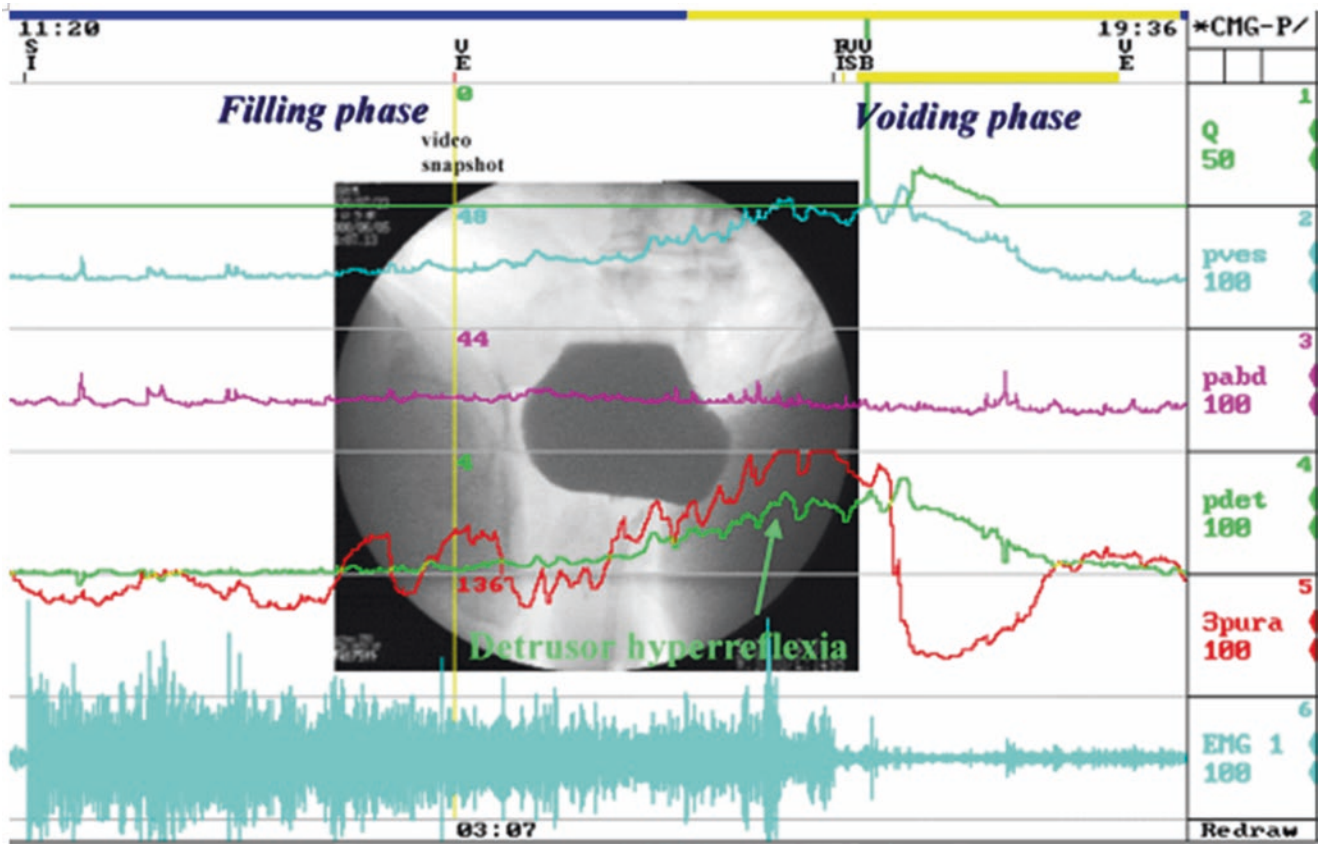

Fig. 65.4 Bladder overactivity

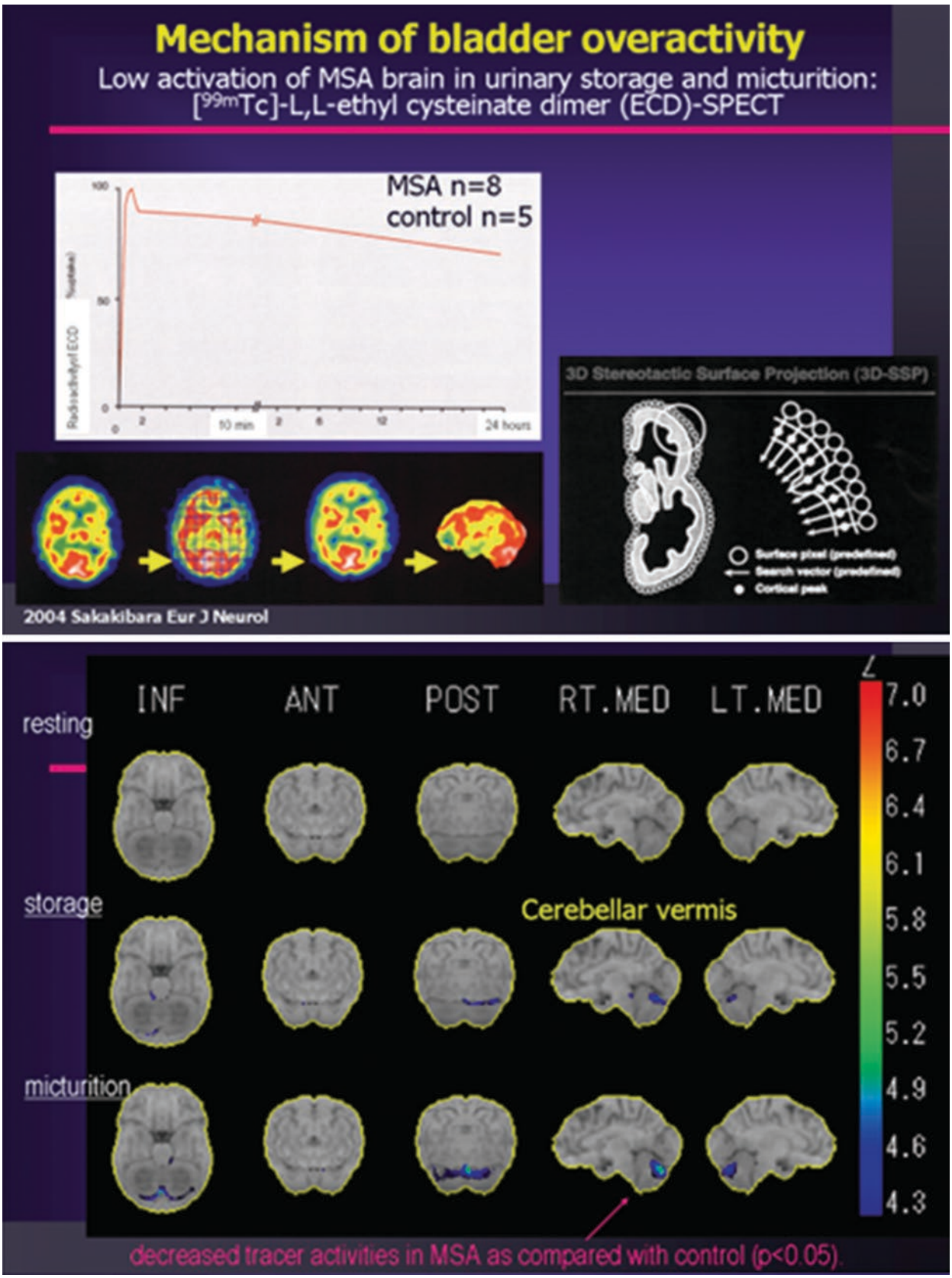

Fig. 65.5 Reduced cerebellar vermis activation in urinary storage and micturition phases in MSA (cite from [37])

65.3.2 Bladder Underactivity and Detrusor-Sphincter Dyssynergia

Incomplete bladder emptying is a significant feature in MSA. In fact, 47% of patients with MSA had post-void residuals (PVR) >100 mL, whereas no patients with IPD had such levels ($p < 0.01$) [19]. The mean PVR volume was 71 mL in the first year, 129 mL in the second year (which exceeded the threshold volume for the start of clean intermittent catheterization (CIC)), and 170 mL in the fifth year from the onset of illness (Fig. 65.6) [38].

Factors relevant to voiding disorder in MSA include the bladder and the urethral outlet. Pressure-flow analysis refers to the simultaneous monitoring of detrusor pressure and urinary flow, and to drawing the relation curve between them. Although it was originally developed for diagnosing outlet obstruction due to prostatic hypertrophy [39, 40]. pressure-flow analysis is useful for evaluating neurogenic voiding difficulty [41].

Pressure-flow analysis showed that bladder underactivity (a weak detrusor contraction) during voiding is more common in MSA (71% in women and 63% in men) than in IPD (66% in women and 40% in men) [19]. The AG number represents a grade of urethral obstruction, and an AG number >40 means outflow obstruction in men [39]. The mean AG numbers were smaller in patients with MSA (12 in women and 28 in men) than in those with IPD (40 in women and 43) [19]. However, a subset of patients with MSA may have an obstructive pattern, the reason for which is unknown. Detrusor-external sphincter dyssynergia is a factor contributing to neurogenic urethral relaxation failure [41], which is noted in 47% of MSA patients [19, 42]. Therefore, it is likely that bladder underactivity accounts mostly for voiding difficulty and elevated PVR in MSA. A subset of patients with MSA has bladder overactivity during storage and underactivity during voiding (detrusor hyperactivity with impaired contractile function, DHIC) [42]. The exact mechanism of this phenomenon has yet to be ascertained. However, it has been recognized that the central mechanisms underlying bladder filling and voiding are distinct from each other; i.e., the area promoting micturition is located in the PMC and the frontal cortex, whereas that promoting urinary storage is in the pontine storage center, basal ganglia, raphe, and frontal cortex [23]. Lesions in these areas may cause various combinations of urinary filling and voiding disorders, such as DHIC.

65.3.3 Role of the Sympathetic System

65.3.3.1 Open Bladder Neck Suggesting Sympathetic Denervation

The bladder neck, also known as the internal (smooth) urethral sphincter, is a component in the maintenance of continence that is innervated by the sympathetic hypogastric nerve. Videourodynamic study is an established method for evaluating bladder neck function. It is a combination of visualizing the lower urinary tract simultaneously with EMG-cystometry; urethral pressure at the external urethral sphincter can be obtained with visual guidance using a radiopaque marker. In normal subjects, the bladder neck is closed

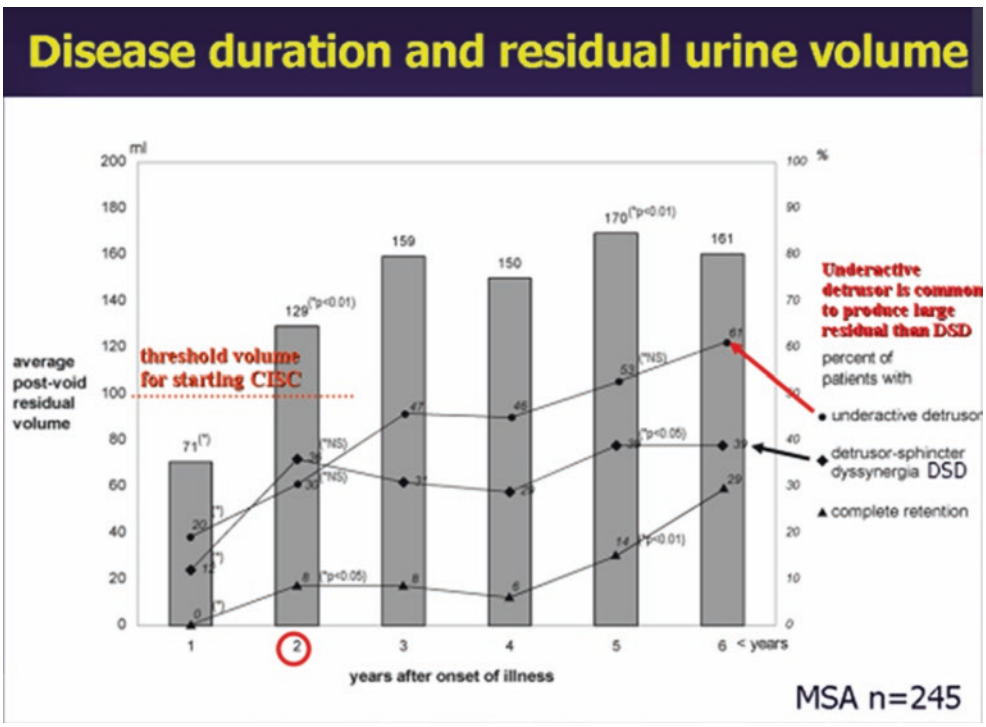

Fig. 65.6 Incomplete bladder emptying in MSA (cited from [38])

throughout filling so as to avoid leaking. However, an open bladder neck is found in 46–100% of MSA patients and in 23–31% of PD patients, and an open bladder neck at the start of bladder filling, even without the accompaniment of bladder overactivity, was noted in no PD patients but in 53% of MSA patients ($p < 0.01$) (Fig. 65.7) [19]. Because open bladder neck is common in patients with myelodysplasia or a lower thoracic cord lesion at T12-L2 (where sympathetic thoracolumbar intermediolateral [IML] nuclei are located) and is reproduced by systemic or intraurethral application of alpha1-adrenergic blockers [43], it is likely that an open bladder neck reflects the loss of sympathetic innervation. This seems to be one of exceptions to primary preganglionic pathology in MSA. An open bladder neck is usually considered asymptomatic, but may cause incontinence and reduce bladder capacity.

65.3.4 Role of the Somatic System

65.3.4.1 Neurogenic Changes in Sphincter EMG Suggesting Somatic Denervation

A distinguishing pathology in MSA is neuronal cell loss in the Onuf nucleus, a group of anterior horn cells in the sacral spinal cord [6]. The first reports on neurogenic changes of external anal sphincter (EAS)-electromyography (EMG) in MSA are attributed to Sakuta et al. (1978) [44]. Since then, EAS-EMG results for over 600 MSA patients have been reported, with abnormality rates of more than 70% in many studies [45, 46]. EAS-EMG is better tolerated and yields identical results to those from EUS investigation [47]. Abnormalities have also been recorded in the bulbocavernosus muscles in MSA [48]. Figure 65.8 shows the method of sphincter EMG in clinical practice. A particular importance is not to miss the late components [21].

In our study of 84 probable MSA cases, 62% exhibited neurogenic change [44]. The prevalence was relatively low presumably because up to 25% of our patients had a disease duration of 1 year or less. In such early cases, the diagnosis of MSA should be made with extreme caution. In addition to the clinical diagnostic criteria, we usually add an imaging study and we perform gene analysis to the extent possible. The prevalence of neurogenic change was 52% in the first year after disease onset, which increased to 83% by the fifth year ($p < 0.05$) (Fig. 65.9a). Therefore, as expected, it is apparent that the involvement of Onuf's nucleus in MSA is time-dependent; and EAS-MUP abnormalities can distinguish MSA from idiopathic Parkinson's disease (PD) and other diseases in the first 5 years after disease onset. Receiver-operating characteristic analysis of sphincter EMG showed

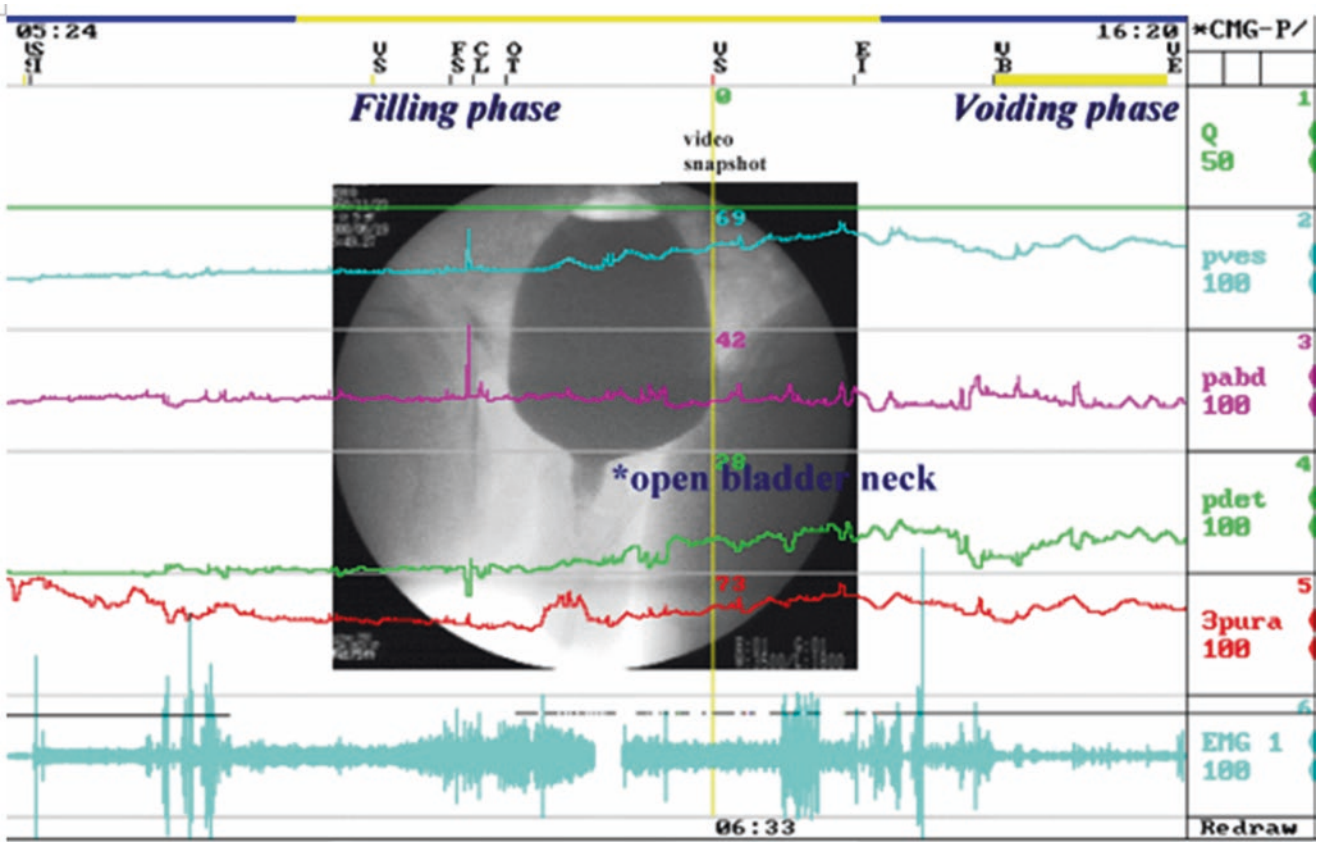

Fig. 65.7 Open bladder neck

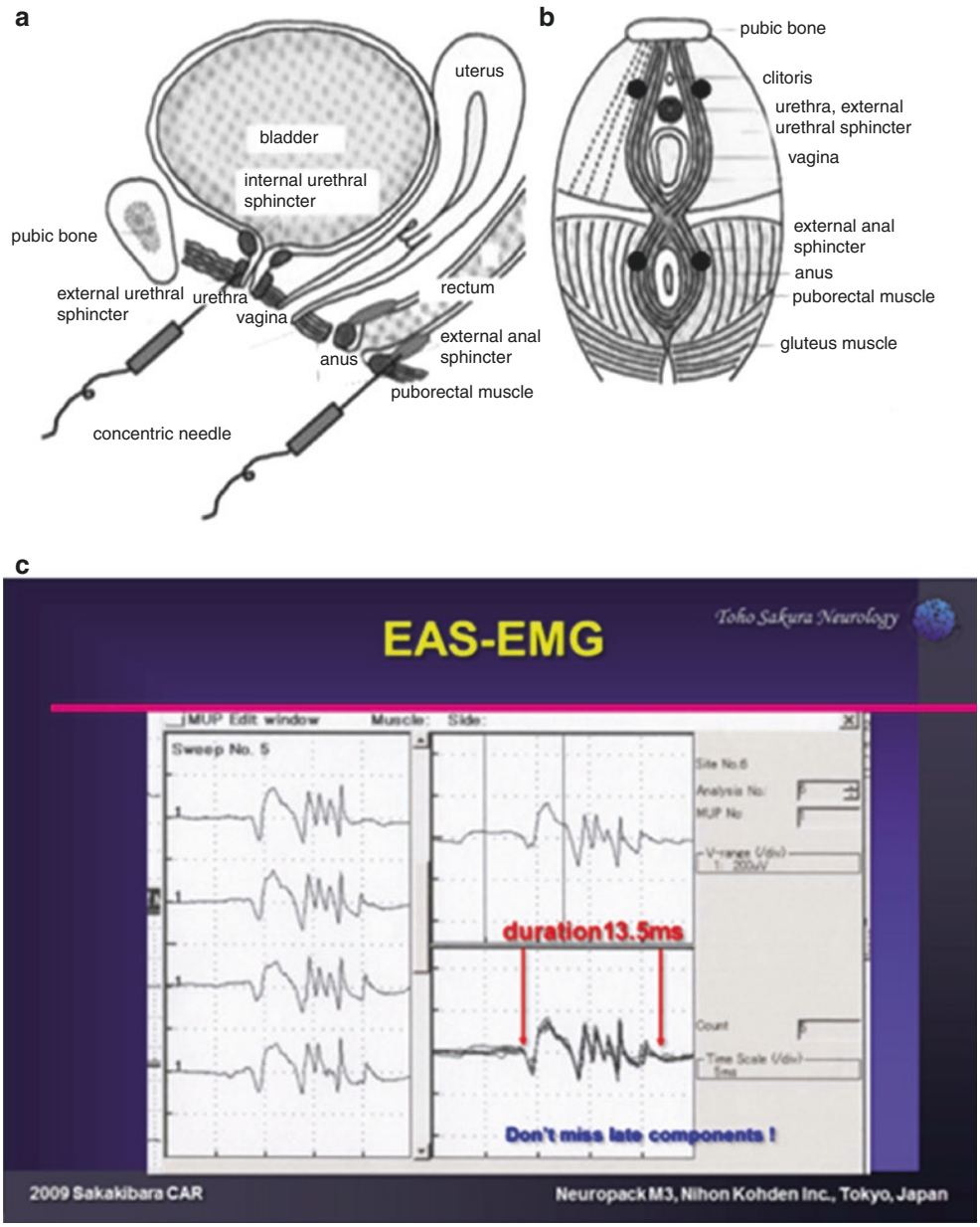

Fig. 65.8 External sphincter EMG. The external anal sphincter and the external urethral sphincter. (**a**, **b**) This figure illustrates where to insert concentric needles to measure external sphincter EMG. (**c**) A motor unit recorded from the anal sphincter of a patient with multiple system atrophy shows an abnormally prolonged duration (upper range of normal is <10 ms) and stable low-amplitude late components (*D* division, *EMG* electromyography, *MU* motor unit) (cited from [45])

high diagnostic power in terms of the duration of motor unit potential (MUP) analysis (Fig. 65.9b) [46].

In contrast, in the early stages of illness, the prevalence of neurogenic change in MSA does not seem to be high. In only 2 patients who underwent repeated studies, the EAS-EMG findings tended to remain normal. We do not know whether some MSA patients never develop neurogenic change during the course of their illness. However, Wenning et al. (1994) reported 3 patients with normal EAS-EMG and a postmortem confirmation of MSA [14]. Therefore, a negative result cannot exclude a diagnosis of MSA. Paviour et al. (2005) reported that among 30 sets of clinical data and postmortem confirmation in MSA cases with a duration of more than 5 years, 24 (80%) had abnormal EAS-EMG, 5 (17%) had a borderline result, and only 1 had a normal EMG [49]. It has been reported that neurogenic change does not correlate directly with a clinically obvious functional deficit, although urinary incontinence was more severe in the patients with neurogenic change than in those without it ($p < 0.05$).

The prevalence of neurogenic change also increased with the severity of gait disturbance (wheel chair bound) ($p < 0.05$) in our study [44]. However, neurogenic change was not related to postural hypotension (reflecting adrenergic nerve dysfunction); erectile dysfunction in men (presumably reflecting cholinergic and nitrate oxidergic nerve dysfunction); detrusor overactivity (reflecting the central type of detrusor dysfunction); constipation (presumably reflecting

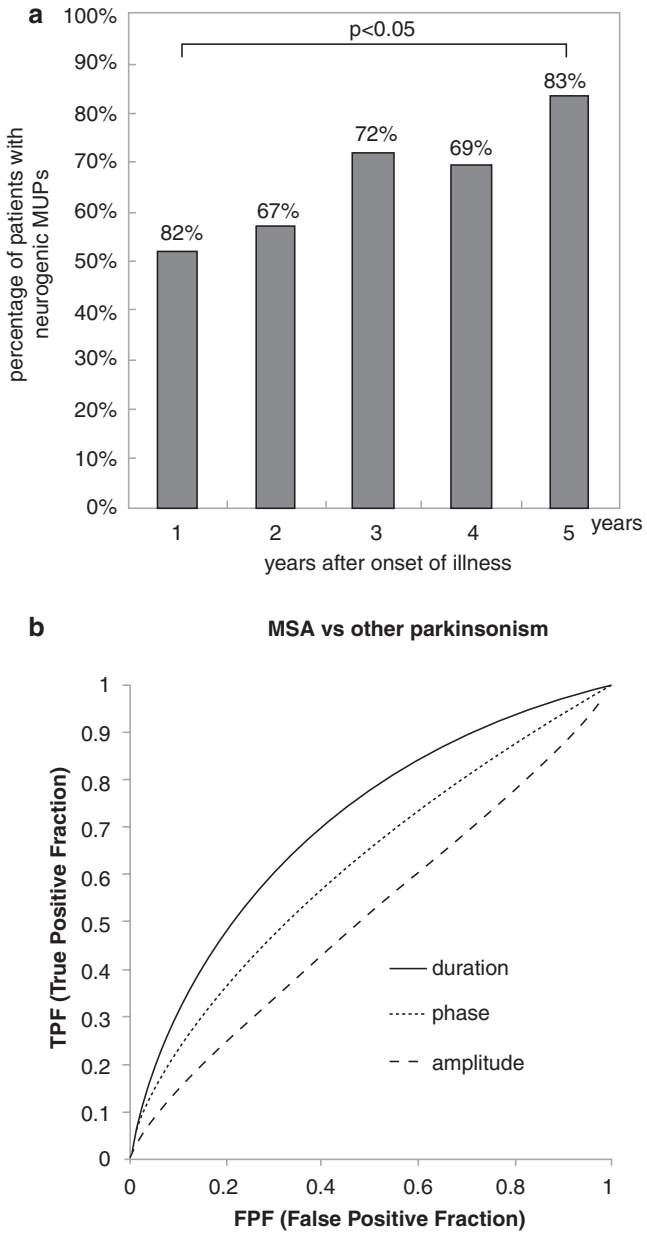

Fig. 65.9 Neurogenic sphincter EMG in MSA. (**a**) The prevalence of neurogenic sphincter EMG increased during the course of illness. *MUP* motor unit potential (cited from [44]). (**b**) Receiver-operating characteristic analysis of sphincter EMG. This figure indicates high diagnostic power in terms of the duration of motor unit potentials (cited from [46])

both peripheral and central types of autonomic and somatic dysfunction); or gender [44]. The neurogenic change in EAS-MUP was slightly more common in those with detrusor-sphincter dyssynergia (DSD). More recently, it is suggested that not only suprasacral pathology, but also sacral/peripheral lesions can produce DSD [50].

Although denervation can be found in the other skeletal muscles in MSA, it occurs much earlier in the external sphincter muscles [51]. This is in clear contrast to the case in amyotrophic lateral sclerosis, where denervation occurs in most advanced cases (respirator bound).

65.3.5 Changes of Bladder Patterns

Bladder patterns change from central to peripheral. The sites responsible for cardiovascular autonomic failure in MSA are mostly central, in contrast to the peripheral lesions in PAF [10].However, 31–45% of patients with MSA also had low-compliance detrusor, defined as a maximum bladder capacity/tonic detrusor pressure increase <20 mL/cmH_2O [13]. Low-compliance detrusor is known to occur in patients with spina bifida or in animals with experimental cauda equina lesions, most probably reflecting neuronal loss of bladder preganglionic neurons in the sacral IML nucleus and their fibers (pelvic nerve) [52, 53]. The bethanechol test is the established method to detect lesions in the most peripheral site [54]. A minimum amount (2.5 mg) of bethanechol, a cholinergic agent, is injected subcutaneously; this amount is not sufficient to evoke bladder contraction in normal subjects. However, when the bladder is denervated, cholinergic receptor densities in the postsynaptic membrane increase, increasing abnormal detrusor pressure upon bethanechol injection. Nineteen percent of MSA patients showed denervation supersensitivity of the detrusor [13].

Repeated urodynamic studies in MSA patients showed that the cystometrogram changed from bladder overactivity to low-compliance or atonic detrusor, and from negative to positive bethanechol supersensitivity [13]. In fact, as the disease progresses, symptoms may change from urinary urgency and frequency to those due to incomplete bladder emptying [12]. These findings suggest that the responsible sites of the bladder cholinergic disorder may change from the ‘center’ (supra-nuclear) to the ‘periphery’ (nuclear sacral IML and/or infra-nuclear) during the course of the illness. Since MSA primarily affects the preganglionic neurons in the autonomic nervous system [10], bladder findings that suggest postganglionic lesions might reflect trans-synaptic degeneration of the cholinergic fibers.

65.3.6 Nocturnal Polyuria

Nocturnal polyuria also occurs suggesting hypothalamic dysfunction. Besides bladder disorders, patients with MSA may have nocturnal polyuria, which results in nocturnal urinary frequency and morning hypotension. In normal children over 7 years and adults, the circadian release of arginine vasopressin (AVP) from the posterior pituitary gland into plasma peaks at night. This leads to a nocturnal decrease in urine formation. The ratio of nighttime to daytime urine production is usually <1:2, which can be estimated by a fre-

quency volume chart. This circadian rhythm can be impaired in cases of congestive heart failure, nephrosis, or cirrhosis with ascites. However, a postmortem study of the brains of patients with MSA revealed the degeneration of AVP neurons in the suprachiasmatic nucleus [48], leading to impairment of the circadian rhythm of the plasma AVP concentration in MSA [55, 56]. In addition, daytime postural hypotension may also cause nocturnal polyuria in patients with MSA [57]. This is probably due to a combination of factors that include compensatory supine hypertension at night, leading to increased glomerular filtration.

65.4 Management of Urinary Dysfunction

65.4.1 Clean, Intermittent Catheterization for Incomplete Bladder Emptying

More than half of patients with MSA have urinary dysfunction either prior to or at the time of presentation with motor disorder. Since many of these patients develop incomplete bladder emptying, they may be misdiagnosed as having prostatic hypertrophy. In fact, the results of urological surgery are rarely favorable, since bladder underactivity contributes more to voiding difficulty than does outflow obstruction. Therefore, it is important to avoid inappropriate urological surgery in patients with MSA [10]. In men with MSA, effects of transurethral resection of the prostate lasted for less than 2 years [38]. A conservative approach with medical measures to manage urinary problems can be effective.

Estimation of the PVR volume is a simple and useful test in patients with MSA; even though their urinary complaints are solely urinary urgency/frequency, they may be unaware that their bladders do not empty completely. PVR can be measured by ultrasound echography, either with specific machines (bladder manager BVI3000, e.g.), abdominal echography (multiplied 3-direction diameters*0.5) or transurethral catheterization. If the patient has a significant PVR and is symptomatic, this aspect of the problem should be managed using CIC performed by either the patient or the caregiver. However, in patients with advanced disease and severe neurological disability, a permanent indwelling catheter, either transurethral or suprapubic, or urosheath drainage may be required.

65.4.2 Drugs to Lessen Bladder Overactivity

The bladder is innervated by the parasympathetic pelvic nerve and has an abundance of $M_{2/3}$ muscarinic receptors. Bladder overactivity may reflect an increased micturition reflex via either the brainstem or the sacral cord, which can be treated with anticholinergic medication such as tolterodine, oxybutynin, propiverine, or propantheline. These drugs diminish the parasympathetic tone on bladder smooth muscle, and are usually tried in patients with urinary urgency and frequency. However, anticholinergic side-effects, particularly dry mouth (probably mediated by M_3 receptors) and constipation ($M_{2/3}$ receptors), may limit their use in a proportion of the patients. A subset of patients with MSA may develop mild cognitive decline at an advanced stage of the disease. Since the use of anticholinergic drugs carries a risk of cognitive impairment (M_1 receptors) [58], though this is much less common than the drugs' peripheral effects, we have to be careful to manage urinary dysfunction in such patients. Anticholinergic drugs do ameliorate urgency and frequency, but may also reduce bladder contractility during voiding [11]. Therefore, PVR should be measured and if it exceeds 100 mL, the medication should be withdrawn or preferably CIC should be added. If nighttime urinary urgency/frequency is the problem, a night balloon is a good alternative to drugs for patients who are performing CIC [38].

65.4.3 Interactions Between Drugs to Treat Bladder, Postural Hypotension, and Motor Disorder

65.4.3.1 Alpha-Adrenergic Receptors

Since incomplete bladder emptying in patients with MSA is due mostly to bladder underactivity, drugs acting on outflow obstruction are unlikely to benefit all patients. However, in some patients, alpha-adrenergic blockers may be effective in lessening PVR volumes, due probably to detrusor-sphincter dyssynergia [59]. Uro-selective blockers such as tamsulosin and naftopidil may be of choice because they have fewer side-effects such as postural hypotension. The effects of alpha-adrenergic blockers lasted for less than 2 years [38].

In contrast, the drugs most commonly used to treat postural hypotension in MSA are adrenergic agonists. However, administration of amezinium, an adrenergic drug, may increase the risk of retention and PVR volume compared to that before treatment [60]. Amezinium most probably stimulates the alpha receptors, both in the vascular wall ($alpha_{1B}$ receptors, particularly in the elderly [61]) and the proximal urethra ($alpha_{1A/D}$-adrenergic receptors).

65.4.3.2 Cholinergic Receptors

Both postural hypotension and bladder dysfunction are common clinical features in MSA. Pyridostigmine, an acetylcholinesterase inhibitor, can be effective in lessening PVR volumes, since it stimulates muscarinic acetylcholine receptors on the bladder (M2/3-muscarinic receptors) that are innervated by parasympathetic cholinergic neurons [62]. Pyridostigmine also lessens postural hypotension, presumably by enhancing nicotinic acetylcholine receptor transmission in the sympathetic ganglia [63, 64].

65.4.3.3 Dopaminergic Receptors

Whether centrally acting drugs, such as pergolide (a dopaminergic $D_{1/2}$-receptor agonist) for parkinsonism, might ameliorate urinary dysfunction in MSA has not been fully studied [65, 66]. Early untreated IPD patients with mild urgency and frequency tend to benefit from levodopa ($D_{1/2}$) treatment. However, in a 1-h time window, levodopa may augment bladder overactivity in early [67] or advanced [68] IPD patients. Since D_1 selective stimulation inhibits the micturition reflex whereas D_2 selective stimulation facilitates it, the balance of these stimulations may explain the various effects of the drugs. Levodopa ($D_{1/2}$) and its metabolites, such as norepinephrine (noradrenaline), may also contract the bladder neck by stimulating alpha1adrenergic receptors [60].

65.4.3.4 Nocturnal Polyuria (Vasopressin Receptors)

Desmopressin is a potent analogue of AVP (hypertensive and antidiuretic effects: 100 vs. 100 in AVP; 0.39 vs. 1200 in desmopressin, respectively), and it is used in the treatment of diabetes insipidus due to a loss of posterior pituitary AVP secretion. Mathias et al. [56] used 2–4 μg of intramuscular desmopressin in patients with autonomic failure including MSA. We also prescribed 5 μg of intranasal desmopressin once a night in MSA patients with impaired circadian rhythm of AVP and nocturnal polyuria, with benefit [69]. This small dose of desmopressin is unlikely to cause adverse effects. But hyponatremia and signs of cardiac failure should be checked for regularly. A tablet form is available and may be more convenient for patient use. Desmopressin could also ameliorate morning hypotension resulting from the abnormal loss of body fluid at night [56].

65.4.4 Micturition Syncope

Well-known triggers for syncope in MSA include: (1) standing (postural syncope), (2) eating (post-prandial syncope), and (3) exercise (post-exertional syncope) [10]. We found that syncope in patients with MSA is also triggered by (4) voiding (micturition syncope). In our patients, the systolic blood pressure increase was less pronounced during storage, whereas the systolic blood pressure decrease was significant during and after voiding as compared with control [70]. The detailed link between the bladder and the cardiovascular system is still uncertain in this condition. However, particularly in patients who experience abdominal strain upon voiding, CIC could lessen micturition syncope.

65.4.5 Bladder Management and Survival

Recent studies suggest that bladder management may directly, or indirectly, affect survival of MSA [71, 72]. Coon et al. suggested that while the initial onset with autonomic symptoms was not associated with shortened overall survival, early autonomic symptoms in disease course, particularly bladder symptoms and severe urinary symptoms (requiring urinary catheterization), negatively affected survival [71]. Since MSA is a progressive disease that leads to urinary retention, early differential diagnosis from Parkinson's disease is necessary in terms of catheterization [73, 74].

65.5 Summary

Urinary dysfunction is a prominent autonomic feature in patients with MSA, and it is more common (above 90%) and occurs earlier than postural hypotension in this disorder. Since the clinical features of MSA may mimic those of IPD, a distinctive pattern of urinary dysfunction in both disorders is worth looking at. In contrast to IPD, MSA patients have more marked urinary dysfunction, which consists of both urgency incontinence and post-void residuals >100 mL. Videourodynamic and sphincter EMG analyses are important tools for understanding the extent of these dysfunctions and for determining both the diagnosis and management of the disorders. The common finding in both disorders is bladder overactivity, which accounts for urinary urgency and frequency. However, detrusor-sphincter dyssynergia, open bladder neck at the start of bladder filling (internal sphincter denervation), and neurogenic sphincter EMG (external sphincter denervation) are all characteristics of MSA. These features may reflect pathological lesions in the basal ganglia, pontine tegmentum, raphe, intermediolateral cell column, and sacral Onuf's nuclei. During the course of the disease, the pathophysiological balance shifts from central to peripheral, with bladder emptying disorder predominating.

Since MSA is a progressive disorder and impaired detrusor contractility is common, it is important to avoid inappropriate urological surgery in patients with MSA. A conservative approach with medical measures includes anticholinergics for urinary urgency and frequency, desmopressin for nocturnal polyuria, uro-selective alpha-blockers and cholinergic stimulants for voiding difficulty, and CIC for large PVR.

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Disc Disease

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Disc disease encompasses a variety of vertebral disorders including disc degeneration and herniation. Up to 80% of people will experience back pain over their lifetime and this can commonly be associated with degeneration of the intervertebral disc [1]. Degenerative disc disease is the clinical syndrome described by manifestations thought to be related to disc degeneration, characterized broadly by fissures, degeneration, and herniation. Disc herniation is the displacement of disc material, such as nucleus pulposus, beyond the disc edge [2]. Disc herniation occurs most commonly during the third and fourth decades of life with the most common levels of disc herniation being L4–L5 and L5–S1 [3]. Although lumbar disc herniation is the most common, cervical and thoracic discs can also herniate. The level and degree of disc herniation will affect patient symptoms.

Voiding abnormalities are present in 27–68% of patients undergoing surgery for disc disease [4]. Direct compression of the spinal cord and lumbar and/or sacral nerve roots, in addition to local inflammatory effects, can result in lower urinary tract dysfunction (LUTD). Specifically, this can lead to functional bladder changes, including neurogenic detrusor overactivity (NDO) in the early stages, progressing to neurogenic bladder later [4]. The objective of this chapter is to review the relevant neuroanatomy, physiology, clinical presentation and diagnosis of disc disease and potential effects on the lower urinary tract. We will also highlight management options for LUTD secondary to disc disease.

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66.1 Spinal and Vertebral Anatomy

The vertebral column is composed of 7 cervical, 12 thoracic, 5 lumbar, and 5 sacral vertebrae and the coccyx. Between each two vertebrae is an intervertebral disc composed of an inner gelatinous nucleus pulposus surrounded by an outer fibrous annulus fibrosus. A disc is named based on the vertebra immediately above and below. For example, the disc between the fifth lumbar vertebrae and first sacral vertebral body is called "L5–S1" [2].

The spinal cord lies within the vertebral canal. At the level of the T12 vertebral body, the spinal cord becomes conical in structure and is termed the conus medullaris. The conus medullaris tapers to form the filum terminale. Distal to the filum terminale, at the level of the L2 vertebral body, are a collection of nerve roots, called the cauda equina.

There are three types of disc herniation based on the location of protrusion: intraforaminal, posterolateral, and central. Disc herniation usually occurs in a posterolateral orientation where the posterior longitudinal ligament is weakest [3]. Central or midline lesions can compress the anterior portion of the spinal cord. A central disc herniation of the lumbar spine may compress the cauda equina causing cauda equina syndrome. Disc herniation at L4–L5 will most often compress the fifth lumbar root and herniation of L5–S1 usually compromises the first sacral nerve root. However, variations in root anatomy as well as the direction (ex. posterolateral or central) of the herniation can affect these relationships [3].

66.2 Micturition Pathophysiology

Micturition is a coordinated event consisting of sphincter relaxation, detrusor contraction, and bladder neck opening, which is initiated by the pontine micturition center and coordinated through autonomic and somatic nervous systems. The parasympathetic pelvic nerves originate from the sacral spine and provide excitatory signals to the bladder. Sympathetic pathways along the hypogastric nerves arise

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_66

from the thoracic and lumbar spine sending inhibitory signals to the bladder and excitatory input to the urethra and trigone. The somatic nerves to the bladder, specifically the pudendal nerve, arise from sacral segments of the spinal cord and control the external urethral sphincter and pelvic floor musculature. Afferent activity from the bladder and urethra travels to the spinal cord along the pudendal, pelvic, and hypogastric nerves.

When considering relevant neuroanatomy and bladder physiology, it becomes clear that disc disease may affect bladder function. Suprasacral lesions can result in NDO with detrusor sphincter dyssynergia (DSD). Disc disease above the lumbar spine may affect sympathetic innervation (T11–L2). Lumbar disc prolapse may specifically affect the sacral cord interfering with parasympathetic and somatic innervation leading to detrusor areflexia and sphincteric dysfunction [5]. Independent of the level of disc involvement, altered detrusor compliance and upper urinary tract damage may result. The resultant LUTD from disc disease can significantly affect patients' quality of life.

66.3 Patient Presentation and Lower Urinary Tract Evaluation

66.3.1 Clinical History

Clinically, the most common complaint of patients with disc disease is pain, which may radiate the length of the affected nerve root (e.g. sciatica). Other symptoms may include paraspinal muscle spasms and/or neurologic sequela such as numbness and weakness and urinary and/or bowel dysfunction. Symptoms will vary depending on the degree and level of spinal cord or spinal root involvement. The onset of symptoms may be acute or gradual and vary with intensity depending on activity. Additionally, patients should be questioned about the presence of voiding or bowel symptoms prior to the onset of their back symptoms. In addition to voiding dysfunction and fecal incontinence, patients with lumbar disc herniation may also experience sexual dysfunction, which should be considered in the overall care of the patients, but is beyond the scope of this chapter [6].

Although there are variations in the definition of cauda equina syndrome (CES) in the literature [7], clinical features of CES include low back pain, saddle anesthesia, motor weakness, and bladder and bowel dysfunction. CES due to lumbar disc herniation is relatively rare with an estimated incidence of 2–3% of all cases of herniated lumbar discs [8, 9]. CES can be classified as complete or incomplete based on the presence of urinary retention and perianal sensory loss in complete CES [10]. Patients with incomplete CES may have voiding symptoms including altered bladder sensation or urgency or may not have any voiding dysfunction. In a study of patients undergoing MRI for back pain, no single clinical feature could predict the presence of CES, highlighting the variable presentation of this syndrome [11].

The prevalence of lower urinary tract symptoms in patients undergoing surgery for disc disease is reported to be 27–68% [4]. Patients should be questioned about overactive bladder symptoms including urinary frequency, urgency with or without incontinence, and nocturia. Patients may have obstructive voiding symptoms or the feeling of incomplete emptying in instances of detrusor areflexia. Patients may complain of urinary incontinence and careful questioning may help to elucidate if this is a stress urinary incontinence due to sphincter dysfunction or an urge urinary incontinence from detrusor overactivity. In some instances, painless urinary retention may be the only presenting symptom of patients with central lumbar disc prolapse [12]. However, more commonly, patients initially experience back pain prior to the onset of voiding dysfunction, and the duration from onset of initial disc disease-related symptoms to voiding dysfunction is variable, ranging from 3 days to 5 years in one study [13].

66.3.2 Physical Examination

In addition to a thorough genitourinary examination, patients presenting with voiding dysfunction secondary to disc disease need a careful neurologic examination. This should include assessment of sensation to both light touch and pinprick. Sensory loss on the lateral foot can be isolated to S1–S2 and sensory loss of the perineum or perianal area involves S2–S3 nerve roots. Also, with sacral root compression, patients may have loss of reflexes. Specifically, if the first sacral root is compressed, patients may have difficulty rising up on their toes due to weakness of the gastrocnemius-soleus muscle complex. Depressed patellar tendon and Achilles tendon reflexes can be caused by compression of L3–L4 and L5–S1, respectively. The bulbocavernosus reflex (S2–S4) and anal sphincter should also be assessed. Additionally, atrophy of involved muscle groups may be noted on exam in instances of chronic nerve compression.

66.3.3 Patient Work-up

Following a thorough history and physical examination, the European Association of Urology Guidelines on neurogenic LUTD recommends a voiding diary, urinalysis, serum chemistry, uroflowmetry, and upper tract imaging in patients with neurogenic bladder [14]. Additionally, urodynamic evaluation is felt to be essential in the documentation of LUTD. If video capabilities are available, videourodynamics is preferred to fully document pathology of the lower and upper urinary tract [14].

A voiding diary, completed over 2–3 days, can help elucidate information on frequency of voids, volumes voided, and severity of incontinence. Urinalysis can identify patients with hematuria or urinary tract infection and blood chemistry will give baseline measure of renal function. On uroflowmetry, intermittent pattern in the flow curve may indicate abdominal voiding. In fact, Bartolin et al. demonstrated an intermittent flow pattern in the majority of patients with detrusor areflexia with lumbar disc protrusion who were able to void spontaneously [15].

Urodynamic findings of patients with lumbar disc disease requiring surgery include detrusor areflexia in up to 74% [4, 15]. In patients with neurogenic bladder due to disc disease, urodynamic findings can be correlated to the location of disc herniation. In cervical and thoracic disc disease, the majority of patients had detrusor hyperreflexia with dyssynergia. Patients with lumbar disc herniation and neurogenic bladder most commonly had detrusor areflexia [16]. Specifically, in a study of 122 patients with neurologic sequelae from lumbar disc protrusion, 26% of patients had detrusor areflexia. Seventy-three percent had normal detrusor activity, although a subset of these patients (14%) had high bladder capacity (>500 mL) suggesting altered bladder sensation. In patients with no complaints of lower urinary tract symptoms, all had normal urodynamic findings suggesting that urologic evaluation of patients with lumbar disc disease is not likely to reveal abnormalities in patients without voiding complaints [15].

The upper urinary tract should be evaluated in patients with neurogenic bladder and disc disease as up to 40% may have some degree of upper urinary tract damage [16]. Patients should be evaluated for the presence of vesicoureteral reflux and hydronephrosis, which can be factors predisposing to renal failure. The presence of detrusor sphincter dyssynergia may predict damages to the upper tracts, whose preservation is of upmost importance to prevent long-term renal damage and renal failure.

66.4 Patient Management

66.4.1 Treatment of Disc Disease and Effects on Lower Urinary Tract

In cases where lower urinary tract dysfunction is felt to be attributed to disc disease, it is important to treat the underlying pathology. Approximately 95% of patients with uncomplicated disc herniation will respond to conservative therapy with medications including anti-inflammatories, analgesics, and muscle relaxants and bedrest followed by physical therapy [3, 8]. Epidural steroid injections may also be trialed prior to surgical intervention when non-invasive options have failed [17]. Indications for surgical treatment of disc herniation (i.e. discectomy) include failure to clinically improve after an appropriate conservative trial or neurologic sequelae from nerve compression.

In the case of cauda equina syndrome (CES), characterized by saddle anesthesia, motor weakness, and urinary incontinence, urgent surgical decompression is recommended and can help improve the likelihood of bladder function recovery. In a meta-analysis of surgical outcomes of CES secondary to lumbar disc herniation [8], patients undergoing surgery within 48 h had significantly better resolution of their symptoms, including urinary and rectal incontinence, compared to those undergoing surgery 48 h or more after the onset of symptoms. Patients with a history of chronic lower back pain pre-operatively were 11 times more likely to continue having urinary incontinence after surgery and had 25 times the risk of having rectal dysfunction after surgery. Overall, of the 322 patients included in this meta-analysis, reported outcomes revealed post-operative urinary continence in 73% [8].

Additionally, the distinction between complete and incomplete CES is important for pre-operative planning and discussion with patients. In a study of 200 patients with CES, 63% of patients with incomplete CES had normal bladder function post-operatively compared to only 26% of patients with complete CES. Furthermore, patients with incomplete CES had a higher likelihood for normal bladder outcome depending on the timing of surgery (<24 h vs. >48 h) [10]. Similarly, in a smaller study of 25 patients with complete CES, normal post-operative bladder function was achieved in 36% and, again, was more likely in those patients operated on <48 h after onset of symptoms [9].

Despite appropriate surgical management in patients with disc herniation and LUTD, recovery of normal voiding function after surgery is variable. One hypothesis is that recovery of autonomic nerves affecting bladder function is slower than that of somatic nerves controlling external sphincter activity [13]. In a study of eight patients with acute urinary retention from central lumbar disc prolapse, pre-operative urodynamic assessment demonstrated an acontractile bladder with absent bladder sensation in all patients. Also, most patients showed absent or denervated motor potentials on electromyogram (EMG). Follow up urodynamic evaluation was performed (follow-up range: 1 month to 6 years) and all patients persisted with an acontractile bladder, however some patients did demonstrate improvement in EMG activity.

In addition to the pathology resulting from the disc disease causing bladder dysfunction, consideration must be given to the sequelae of spinal surgery and its potential effects on bladder function. In one series, 60% of patients undergoing discectomy or laminectomy experienced new or worsening urinary symptoms following surgery [18]. Although there are several reasons to explain this finding, such as unmasking of pre-existing urologic pathology, recur-

rence of cord or nerve root compression, worsening of the original disease process, or iatrogenic etiology, it is clear that patients undergoing lumbosacral spinal surgery are at risk for post-operative urinary dysfunction.

In summary, return of urinary continence following surgical decompression is reported to be between 36 and 73% depending on the degree of cord or nerve root involvement and the timing of decompression. EMG activity may improve despite those patients with persistent bladder acontractility. Pre-operative chronic back pain and time to surgical intervention are risk factors for continued urinary dysfunction after surgical decompression. The risk of developing new or worsening post-operative urinary dysfunction following spinal surgery has not been well studied and questions regarding the etiology are not yet answered.

66.4.2 Management of Urinary Tract Dysfunction Related to Disc Disease

For patients with persistent LUTD, the primary goals of bladder management include preservation of upper tract function, maintenance of continence, and restoration of lower urinary tract function while supporting a patient's quality of life. Treatment needs to be individualized based on patient's voiding dysfunction as it relates to their disc disease and other medical comorbidities [14].

Conservative treatment options such as behavioral modifications, pelvic floor muscle exercises, and biofeedback can be tried initially. Behavioral management strategies include timed voiding, controlled fluid intake, and lifestyle changes. Alternative voiding patterns, such as abdominal voiding and crede maneuver may be used, although these are not recommended. Yamanishi et al. showed that despite patients persisting with an acontractile bladder following surgery for disc herniation, all patients could nearly empty their bladder (PVR range: 0–117 mL) with abdominal straining in the absence of detrusor contraction [13]. However, bladder emptying through crede or abdominal straining can have negative effects in the presence of obstruction and should not be employed in patients with high intravesical pressures, ureteral reflux, urethral stricture, or pelvic organ prolapse [19]. Pelvic floor physical therapy may be helpful in selected patients to improve continence and biofeedback can be useful to reinforce voiding pattern modifications [20, 21]. Bladder rehabilitation techniques can aim to restore bladder function through the use of electrical stimulation (e.g. neuromuscular electrical stimulation, intravesical electrostimulation) however high quality evidence is lacking [14].

For patients with detrusor underactivity or areflexia and incomplete bladder emptying, initial management is clean intermittent catheterization. If intermittent catheterization is not possible and the patient is not a candidate for urinary diversion, indwelling catheterization with a suprapubic tube is an option, with patients reporting long-term high satisfaction [22].

To optimize outcomes of patients with voiding dysfunction, often a combination of behavioral management, antimuscarinic medications, and if needed, catheterization is initial therapy for neurogenic LUTD. Antimuscarinic drugs reduce symptoms of overactive bladder and improve bladder capacity and compliance. Specifically, oxybutynin, tropsium chloride, tolterodine, and darifenacin have shown improvement in the treatment of overactive bladder symptoms in neurogenic populations [23]. Titration of drug dosages may be needed for maximum efficacy in this patient population. Newer beta-3 agonist medications, such as mirabegron, have also been shown to have clinical efficacy in urinary frequency and urge urinary incontinence episodes [24, 25] and have shown clinical improvements specifically in patients with NDO from spinal cord injuries [26].

In patients with continued incontinence from NDO despite optimal medical therapy and catheterization, onabotulinumtoxin-A injection into the detrusor is an option and can provide sustained clinical benefits. In a meta-analysis of randomized controlled trials of patients with NDO, intradetrusor injection of 200–300 units of onabotulinumtoxin-A had a significant effect on decreasing urinary incontinence episodes and improving urodynamic parameters, specifically cystometric capacity and maximum detrusor pressure [27].

Sacral neuromodulation is a well-established treatment option for patients with medication refractory urge urinary incontinence and non-obstructive urinary retention. Although it is not approved by the Food and Drug Administration (FDA) for patients with neurogenic bladder, studies suggest that it is a safe and effective option in carefully selected patients with neurogenic bladder. A meta-analysis of studies evaluating sacral neuromodulation for patients with neurogenic LUTD, demonstrated the test phase success rate was 68% and the success rate of subsequent permanent implantation was 92% [28]. However, the definition of success was not specifically defined in this meta-analysis. In a recent, small study of patients with multiple sclerosis and neurogenic LUTD, 94% of patients had a successful test phase. At 3 years follow-up, patients had statistically significant improvements in mean voided volume and post void residual, urinary frequency, and number of incontinence episodes [29].

Posterior tibial nerve stimulation (PTNS), a minimally invasive neuromodulation technique, has shown benefit in management of neurogenic overactive bladder in patients with multiple sclerosis. Specifically, in a study of patients undergoing 12 weeks of PTNS therapy followed by 14 day intervals for 3 months, 21 day intervals for 3 months, and 28 day intervals for 3 months, there was improvements in daytime frequency, nocturia, and urge incontinence episodes over the 1 year period [30].

Another type of neuromodulation, sacral anterior root stimulation with rhizotomy, has been studied in patients with spinal cord injury. Anterior root stimulation is thought to activate parasympathetic pathways to induce detrusor contraction and somatic nerves controlling external urethral sphincter to improve bladder emptying. Rhizotomy can suppress detrusor overactivity and detrusor sphincter dyssynergia. In one cross-sectional study, anterior root stimulation and rhizotomy has been shown to improve quality of life, continence, and urinary tract infection rate [31].

When more conservative measures fail, bladder augmentation and/or urinary diversion may be considered in appropriate patients with small capacity bladder and elevated bladder pressures to restore continence and protect upper tracts.

Newer therapies continue to be developed for patients unresponsive to conventional options. Dorsal penile-clitoral nerve electrical stimulation has demonstrated efficacy in suppressing detrusor contractions in patients with NDO [32, 33]. Ongoing research using human embryonic stem cells injected into the lumbar spine of mouse models demonstrated improvements in bladder dysfunction related to spinal cord injury [34]. This could have future implications in management of patients with bladder dysfunction due to cord compression from disc disease.

66.4.3 Follow-up of Patients with Lower Urinary Tract Dysfunction Related to Disc Disease

Careful and consistent follow-up is required in patients with LUTD to ensure stability of the bladder and protection of upper tracts. Patients should be monitored for urinary tract infections and development of hydronephrosis or nephrolithiasis with upper tract imaging. Additionally, any signs of symptoms indicating a change in bladder function (e.g. worsening urinary incontinence, recurrent urinary tract infections, renal function deterioration) warrants further evaluation as appropriate. Specifically, the European Association of Urology recommends urinalysis and bladder-renal ultrasound every 6 months, annual physical examination with serum and urine testing, and videourodynamics every 1–2 years for patients with neurogenic lower urinary tract dysfunction [14].

66.5 Conclusions

The location and type of disc pathology will influence the extent of bladder dysfunction, but the complexity and variations of the sacral nerve root anatomy can lead to variable clinical presentations. The prevalence of voiding symptoms in patients undergoing surgery for disc disease is 26–74%. Physicians should have a high clinical suspicion of disc disease in patients presenting with back pain and voiding dysfunction. In patients with cauda equina syndrome, prompt diagnosis and surgical decompression are paramount to minimize neural damage and increase likelihood of complete recovery of voiding. Urodynamic evaluation with EMG should be considered for diagnosis of LUTD and to help guide bladder management. Given the high likelihood of persistent voiding dysfunction even after surgical treatment of disc disease, patients should be followed post-operatively. Patients with persistent neurogenic bladder need to be followed long-term given the risk of upper urinary tract damage. There are several management strategies available for neurogenic LUTD with the goal of preserving upper tract function and maintaining continence and quality of life.

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Diabetes

67

Abdulrahman Almuhrij and Riyad Al Mousa

67.1 Introduction

Changes in environmental and behavioral factors such as a sedentary life style and obesity over the previous years have resulted in a dramatic increase in the incidence of diabetes worldwide [1]. Urological manifestations of Diabetic patients include: Diabetic Nephropathy, Renal Vascular disease, Urinary Tract Infections, Emphysematous Complications, Infertility, Erectile dysfunction, and Diabetic bladder dysfunction which we will talk about it in details in this section [2, 3].

The most common and bothersome lower urinary tract complication of diabetes mellitus is diabetic bladder dysfunction (DBD). Although DBD is not life threatening, it affects quality of life substantially. Estimates of the prevalence of bladder dysfunction are 43–87% of type 1 diabetic patients and 25% of type 2 diabetic patients [2–4], a higher rate than that of widely recognized complications such as nephropathy, which affects less than 50% of patients [5, 6]. Even with well controlled blood glucose, the disease incidence would be around 25% [7, 8].

Yet, the treatment modalities of DBD are limited. Understanding DBD pathogenesis is important for development of new options of treatment. Bladder dysfunction can involve different degrees and combinations of diminished bladder filling sensation and poor contractility, which results in an increased post void residual urine, predisposing to infections, lithiasis and ultimately more dangerous conditions like renal damage [6, 8].

67.2 Mechanism of Micturition

The bladder has two main functions, urine storage and urine voiding. Any storage or voiding disorder of the bladder might lead to bladder dysfunction [9]. DBD is characterized by impaired sensation of bladder fullness, which leads to overstretched bladder, reduced bladder contractility, increased residual urine and impaired uroflow [10].

DBD has been described traditionally as a triad of decreased sensation, increased capacity and poor emptying, but many inconsistencies with those traditional findings have been found [11]. Ueda et al. found in most of the asymptomatic diabetic patients they studied that they have an increased bladder volume at first sensation to void and a decrease in detrusor contractility, with resultant increased post void residual urine volume. But, they also found a 25% incidence of detrusor overactivity [12]. Another review by Kaplan et al. of urodynamic findings in 182 diabetic patients revealed 55% with detrusor overactivity but only 23% with impaired contractility, with 10% of patients are areflexic and 11% indeterminate [13]. The mixed clinical picture of DBD has also been revealed in recent large-scale studies, in which diabetes mellitus was associated with a 40–80% increased risk of urge incontinence and a 30–80% increased risk for overflow incontinence in controlled multivariate analyses [14]. All the previous described studies confirm that DBD manifestations are due to a combination of storage and voiding bladder problems (Fig. 67.1).

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L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_67

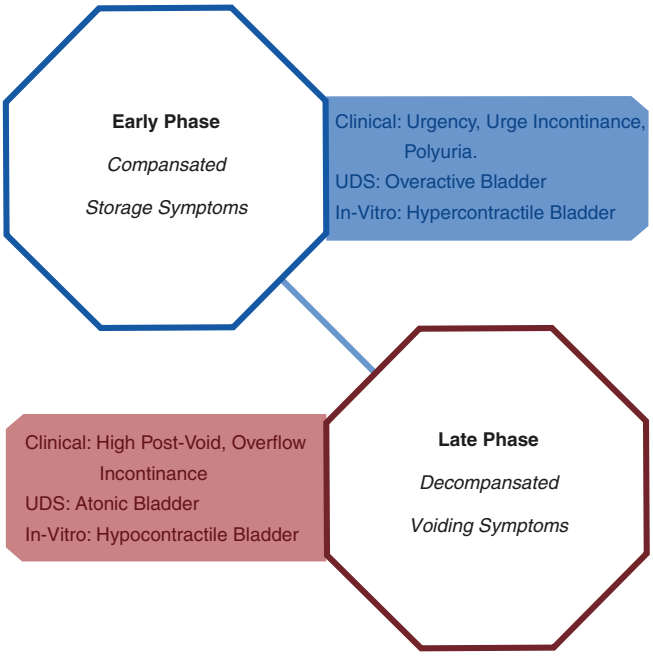

Fig. 67.1 Diabetic bladder dysfunction

67.3 Pathophysiology

Autonomic neuropathy—which results in decreased sensation of the bladder with patient being unaware of bladder filling and lacking desire to empty—was traditionally viewed to be the sole etiology of DBD [15]. Many Investigators found that this view is deficient and that the pathophysiology of DBD is multifactorial, including disturbances of the bladder detrusor, urethra, autonomic nerves, and perhaps the urothelium [16]. Many investigators observed that, upon induction of diabetes mellitus in rodents by destruction of the pancreatic β-cells with streptozotocin, the bladder and urethra undergo morphometric and functional changes in both myogenic and neurogenic components [17–22] while another study has demonstrated the potentially obstructive effects of urethral sphincteric mechanisms in DBD [23].

67.4 Specific: Theories Behind DBD

67.4.1 Neuropathy Injury

DBD is induced by polyneuropathy and that predominantly affects sensory and autonomic nerve fibers [24]. Animal and human studies have revealed that DBD develops as a result of polyneuropathy, which predominantly affects sensory and autonomic nerve fibers [10]. The result of neurogenic lower urinary tract disease depends on the location and duration of the neurologic lesion [25]. Xiaoting Niu and Xun Wang et al. studied bulbocavernosus reflex test on normal and diabetic female subjects and noticed that diabetic patient has more bulbocavernosus reflex latency than non-diabetic subjects, and diabetic patients with disease course >10 years has more bulbocavernosus reflex latency than diabetic patients with disease course <5 years. Their results suggest that the pudendal nerve injury in female diabetic neurogenic bladder patients might occur before limb-nerve injuries as an abnormal bulbocavernosus reflex that could be detected in female DBD patients irrespective of the presence of nerve-conducting study abnormalities [26].

67.4.2 Nerve Growth Factor

Many studies have illustrated that a deficiency in the retrograde axonal transport of nerve growth factor from target organs to sensory pathways may have a role in inducing diabetic neuropathy [27, 28]. This observation leads us to hypothesize that changes in nerve growth factor levels in the bladder and/or bladder afferent pathways could be involved in the bladder dysfunction induced by peripheral neuropathy in diabetes mellitus. A study showed an initial rise in bladder nerve growth factor 1 week after diabetes mellitus induction in rats, followed by a gradual decrease in bladder nerve growth factor levels in a subsequent 3-week period [29].

Katsumi Sasaki et al. found in their study in rats with streptozotocin induced diabetes mellitus a significant time dependent decrease in nerve growth factor levels in the bladder and L6–S1 dorsal root ganglia that was associated with voiding dysfunction attributable to defects in δ and C-fiber bladder afferents [30]. Therefore, reduced production of nerve growth factor in the bladder and/or impaired transport of nerve growth factor to L6 to S1 dorsal root ganglia, which contain bladder afferent neurons, could be an important mechanism inducing diabetic bladder dysfunction.

67.4.3 Bladder Receptors

The neural stimulus of M2 and M3 receptors control the micturition reflex [30].

In diabetic patients, it was found that the number of muscarinic receptors in the urothelium is higher than non-diabetic patients, leading to an increase in the sensory nerve activity that might alter detrusor contraction, which cause further bladder dysfunction [31]. An increase in muscarinic receptor density has been found at both 2 and 8 weeks of streptozotocin induced diabetes [32]. A recent study found an increase in beta 1-receptor–mediated relaxation response in an isolated detrusor smooth muscle strips from 8 to 10 weeks streptozotocin-induced diabetic rats. Also, the abnormalities in the Ca++ and K+ channels that further induce detrusor overactivity [33].

67.4.4 Duration of Diabetes Mellitus

In studying the natural history of diabetic mellitus and bladder dysfunction, Daneshgari et al. proposed the "temporal hypothesis" [11]. It was observed that morphological and functional sequences of DBD are time-dependent. The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease [2, 34]. Bladder hypertrophy, increased contractility and associated neurogenic changes occur soon after the onset of diabetes mellitus [2, 17, 18] while the drop of peak voiding pressure in the cystometric measure develops only at a later stage of diabetes mellitus [35, 36] (Fig. 67.2).

67.4.5 Prolonged Hyperglycemia and Oxidative Stress

When cells are constantly exposed to hyperglycemia for long periods of time, it can cause an accumulation of oxidative stress products; which plays an important role in nerve damage that causes DBD [37]. Oxidative stress in diabetes could originate from a variety of mechanisms, which include: oxygen radical production from auto-oxidations of glucose, glycated proteins, stimulations of cytochrome P450–like activity, alterations of nicotinamide adenine dinucleotide phosphate hydrogen/nicotinamide adenine dinucleotide phosphate [NADPH/NADP] ratio by excess glucose going through the polyol pathway, increased production of super oxide dismutase and increased production of lipid peroxidation [38–40].

67.4.6 Urothelium

The urothelium is an active participant in the normal function of the bladder and it exists as an integral part of a 'sensory web'. The urothelium transmits the degree of bladder filling to the underlying nervous and muscular tissues and affects their functions.

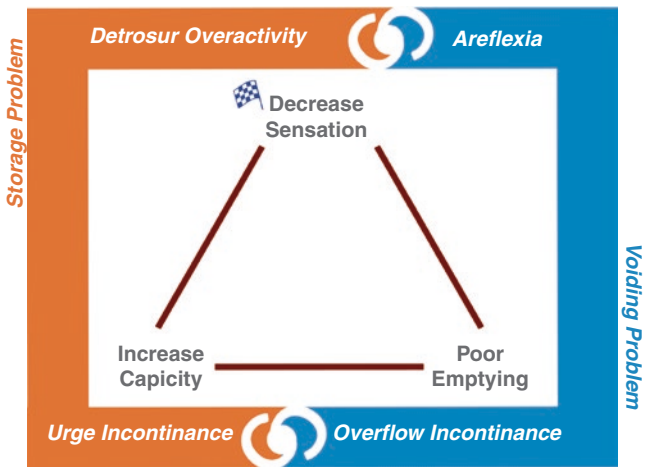

Fig. 67.2 Phases of DBD

Number of studies tackled the effects of diabetes mellitus on bladder urothelium, using the streptozotocin-induced diabetic rat model. These studies have reported an increase in the urothelium proliferation without an increase in the thickness of the urothelial lining itself [41, 42]. This increase in proliferation may divert the physiology of the urothelium cells from their normal inter-communication/two-way communication with the underlying bladder tissue, by modifying both urothelial cell receptor expression and the release of signaling molecules such as neurotransmitters. This in turn could impact/modify activity in underlying smooth muscle and nerve endings and could contribute to the bladder function modification observed in diabetes mellitus. It has been reported that urothelial cell prostaglandin release is impaired in streptozotocin-diabetes mellitus rats [43]. Abnormalities in bladder urothelium could impact the lower urinary tract function by altering release of mediators as well as excitability of sensory fibers in the bladder. In addition, because many of these urothelial functions may be altered in diabetes, defects in urothelial cells may explain changes such as detrusor instability and / or changes in bladder capacity [11].

67.4.7 Prostate Enlargement

Diabetes mellitus is frequently associated with benign prostatic hyperplasia, because of the age of incidence. Additionally, bladder dysfunction could cause an increased sympathetic nerve activity and the vascular damage, resulting in further hypoxia in the bladder and prostate, associated with an abnormal cell proliferation that might lead to lower urinary tract symptoms and DBD [43]. One of the potential explanations of the presence of benign prostatic hyperplasia in diabetic patients involves the insulin-like growth factor [44, 45].

67.4.8 Sphincter Dysfunction

The incidence of sphincter dysfunction is about 25% in patients suffering from diabetes for over 10 years, which would increase to more than 50% after 15 years [15]. Urethral sphincter dysfunction was demonstrated as a potential cause in obstructive symptoms in DBD [23].

67.4.9 Polyuria

Unlike most other organs affected by diabetes mellitus, the bladder faces not only hyperglycemia, but also an exceptionally high

volume of urine output. In experimental models, sucrose-induced diuresis causes rapid and substantial bladder hypertrophy and increased bladder contractility, capacity and compliance that are similar to those changes observed in diabetic rats [18, 46]. Those similarities suggest that bladder hypertrophy in diabetic animals may result from a physical adaptation to increased urine production [18, 46]. On the other hand, bladder hypertrophy may also initiate the process of increased oxidative stress [47].

67.4.10 Insulin Treatment

In women with diabetes mellitus, the insulin treatment increases the risk of urge incontinence, compared with the use of metformin which has shown that it does not have any effect in the incontinence [48, 49].

67.5 Clinical Presentation

It was thought that the classic presentation of DBD is the triad of decreased bladder sensation; increased bladder capacity and impaired bladder emptying that ultimately lead to an increase of post void residual [15]. But, more data suggests that patients might experience wide range of voiding symptoms like frequency, urgency, nocturia, urgency incontinence in addition to the above mentioned classic symptoms [37]. It is even believed now that over active bladder symptoms in the form of frequency, urgency and detrusor bladder over activity are more prevalent than decreased sensation, increased capacity and high post void residual [10]. Studies showed that detrusor over activity is present in around 55% of diabetic patients, while detrusor under activity and a contractile bladder are present in 23% and 10% respectively. The presence of the classic triad is more consistent with late presentation and more sever uncontrolled form of the disease [13, 50].

67.5.1 Workup

All diabetic patients with lower urinary tract symptoms, recurrent UTI or incontinence should be evaluated for diabetic bladder dysfunction [37, 50–52]. Workup can be summarized into:

- Full history and Physical examination (mainly to rule out involvement of other conditions like neurological diseases, Benign Prostatic Hyperplasia in men and pelvic organ prolapse in women.
- Voiding diary
- Serum glucose and glycosylated hemoglobin.
- Urine Analysis and culture
- Renal function
- Kidneys and Bladder U/S to assess for upper tract dilatation, and post void residual urine.
- Urodynamic study in the form of filling cystometry and voiding cystometry to fully assess voiding function (which is the cornerstone of assessment and it is usually performed after failure of conservative measures and before the decision for any surgical intervention) [51].

67.6 Management

The aim of management of diabetic bladder dysfunction patients should be directed toward relief of symptoms, improve quality of life and prevent future complications. This can be done by ensuring proper emptying of the blad-

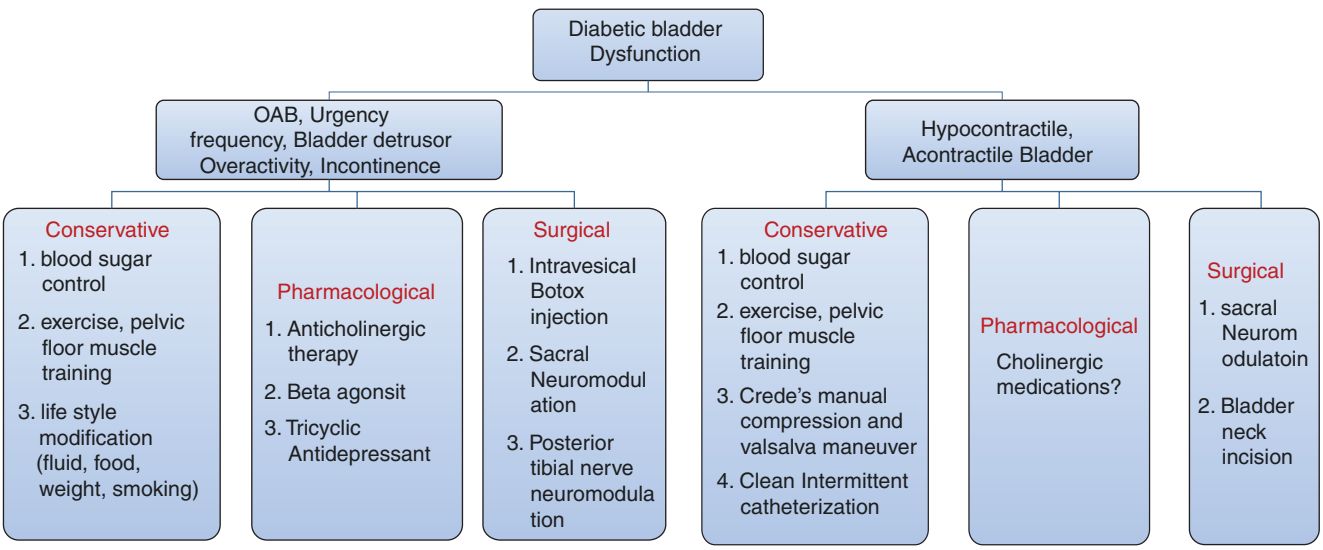

Fig. 67.3 Algorithm for management of DBD

der, treat and prevent urinary tract infection and treat other symptoms and signs according to urodynamic findings.

Treatment options can be classified to three main categories (Fig. 67.3) (which is the standard classification in treating all patients with bladder dysfunction):

- Conservative behavioral therapy.
- Pharmacological therapy.
- Surgical therapy.

67.6.1 Conservative Behavioral Therapy

It should be considered as the first initial step in management of patients with diabetic bladder dysfunction [53, 54].

67.6.1.1 General Therapies

This include:

- Control of blood glucose level.
- Encourage physical activities and exercises.
- Pelvic floor muscle training (Kegel Exercises and PFMT which is helpful to strengthen pubococcygeus muscles which ultimately improves both stress and urge symptoms and this is proven by large randomized trials and systemic reviews)
- Life style modification (fluid manipulation, decrease alcohol consumption, caffeinated beverages and cigarette smoking)

67.6.1.2 According to UDS Findings

Detrusor Over Activity and Incontinence

- Weight reduction: it specifically helps to reduce incontinence rate in patients with diabetic bladder dysfunction. One study showed that only 5–10% weight reduction has a significant positive effect on incontinence rate.
- Fluid manipulation (control of fluid intake especially at night)
- Timed voiding (every 2–4 h) and double voiding (to void twice in order to empty completely)
- Avoid irritative substances (mainly spicy food, citric juices, caffeine and alcohol)

Detrusor Hypo contractility and a Contractile Bladder

- Timed and double voiding
- Use of Crede's manual compression of the lower abdomen or the use of Valsalva's maneuver to facilitate bladder emptying
- Clean self-intermittent catheterization (in those with high post void residual of more than 100 mL or more than 20% of bladder capacity)

67.6.2 Pharmacological Therapy

Mainly to treat patients with overactive bladder and incontinence symptoms as medications have limited role in patients with hypo contractile or a contractile bladder [55–57].

- Anticholinergic medications: they are considered to be the first line drug therapy in treating patients with overactive bladder symptoms, urgency and urge incontinence
- Beta agonists: relatively new group of drugs with promising effectiveness and fewer side effects to treat patients with overactive bladder symptoms.
- Tri cyclic antidepressant drugs: it may enhance bladder relaxation but caution should be taken for serious side effects and dependency.
- Cholinergic medications were tried for patients with bladder hypo contractility to enhance bladder muscle contraction, but their effectiveness was questionable in addition to the marked side effects that limit their daily usage. Bethanechol was tried earlier with limited efficiency to enhance bladder reflex [57].

67.6.3 Surgical Therapy

After failure of conservative therapy and pharmacological therapy, surgical options are the third line of management.

- ***Intravesical Botox injection:*** it has been used widely in patients with neurogenic bladder disorders and currently approved for patients with overactive bladder. The FDA approved dose is 100 International units for OAB patients and 200 IU for those with NBD. It has around 70% success in reducing urgency frequency and incontinence Patients. However, patients must be counseled regarding the risk of urinary retention [58].
- ***Posterior Tibial Nerve Neuromodulations:*** minimally invasive procedure with good efficacy in patients with OAB and urgency frequency syndrome with less information on diabetic patients [59]
- ***Sacral Neuromodulation:*** studies showed that sacral neuromodualtion was effective and successful in both frequency urgency incontinence patients and in patients with non-obstructed urinary retention. Success was similar in diabetic patients but with higher rate of device explantation due to infection [60, 61].
- Other forms of surgical intervention might include: bladder neck incision to reduce outlet resistance but the role is currently unclear especially with newly minimal invasive surgeries as described above [62].

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Radical Pelvic Surgery

68

Paul D. Slocum Jr, Casey G. Kowalik, Joshua A. Cohn, and Roger R. Dmochowski

68.1 Introduction

Radical pelvic surgery is commonly utilized for the treatment of pelvic malignancy. Radical hysterectomy with bilateral pelvic lymphadenectomy is considered the standard of care for the treatment of early invasive cervical cancer, and radical prostatectomy is utilized for the surgical treatment of prostate cancer. Radical hysterectomy for the treatment of locally invasive cervical cancer (stage IB and IIA) involves removal of the uterus, the parametrium (which includes the round, uterosacral, broad, and cardinal ligaments), the upper third of the vagina, and commonly the pelvic lymph nodes. Radical prostatectomy for the treatment of localized prostate cancer involves removal of the prostate, seminal vesicles, and commonly pelvic lymph nodes and has been shown in clinical trials to reduce progression to metastasis and death from prostate cancer [1, 2]. The goals of radical prostatectomy are to eliminate cancer burden while at the same time preserving urinary control and sexual function [3]. Yet, despite the development of nerve sparing techniques and the use of robotic surgery, urinary symptoms may develop as a result of or persist despite these operations. The ensuing chapter seeks to characterize the symptoms and urodynamic findings demonstrated by patients after radical pelvic surgery.

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68.2 Anatomy

A thorough understanding of the pelvic innervation is essential to comprehend the urodynamic changes that can occur as a result of radical pelvic surgery (Fig. 68.1). The pelvic organs and external genitalia receive autonomic innervation from the inferior hypogastric plexus (or pelvic plexus), which receives contributions from the superior hypogastric plexus (via the hypogastric nerves), the sacral splanchnic nerves, and the pelvic splanchnic nerves. The sympathetic fibers originate from the thoracolumbar cord (T11–L2), travel to the superior hypogastric plexus, and enter the pelvis via the hypogastric nerve as they proceed to the inferior hypogastric plexus where they synapse [4–8]. The parasympathetic fibers originate from S2 to S4 and pass through the inferior hypogastric plexus via the pelvic splanchnic nerves. They then proceed to their target organ where they synapse.

In males, the inferior hypogastric plexus lies retroperitoneal beside the rectum approximately 5–11 cm from the anal verge and posteriolateral to the bladder, seminal vesicles, and prostate forming a fenestrated rectangular plate in the sagittal plane 3 (Fig. 68.2). In females, the inferior hypogastric plexus is found posterolateral to the bladder and cervix (Fig. 68.3).

Sympathetic input results in bladder relaxation to facilitate storage and stimulation of the internal urinary sphincter (bladder neck) to remain closed while inhibiting the parasympathetic nervous system. Additionally, somatic pathways control the external striated urinary sphincter via the pudendal nerve. During voiding, sympathetic outflow is inhibited allowing bladder neck relaxation, the external striated sphincter relaxes, and parasympathetic input stimulates bladder contraction to allow coordinated voiding to occur [3].

These neural networks are susceptible to injury upon ligation of the "lateral pedicle" as the vessels to the bladder and prostate penetrate the inferior hypogastric plexus. Injury during ligation can result in damage to the nervous supply of the prostate, urethra, and corpora cavernosa as well as visceral

L. Liao, H. Madersbacher (eds.), *Neurourology*, https://doi.org/10.1007/978-94-017-7509-0_68

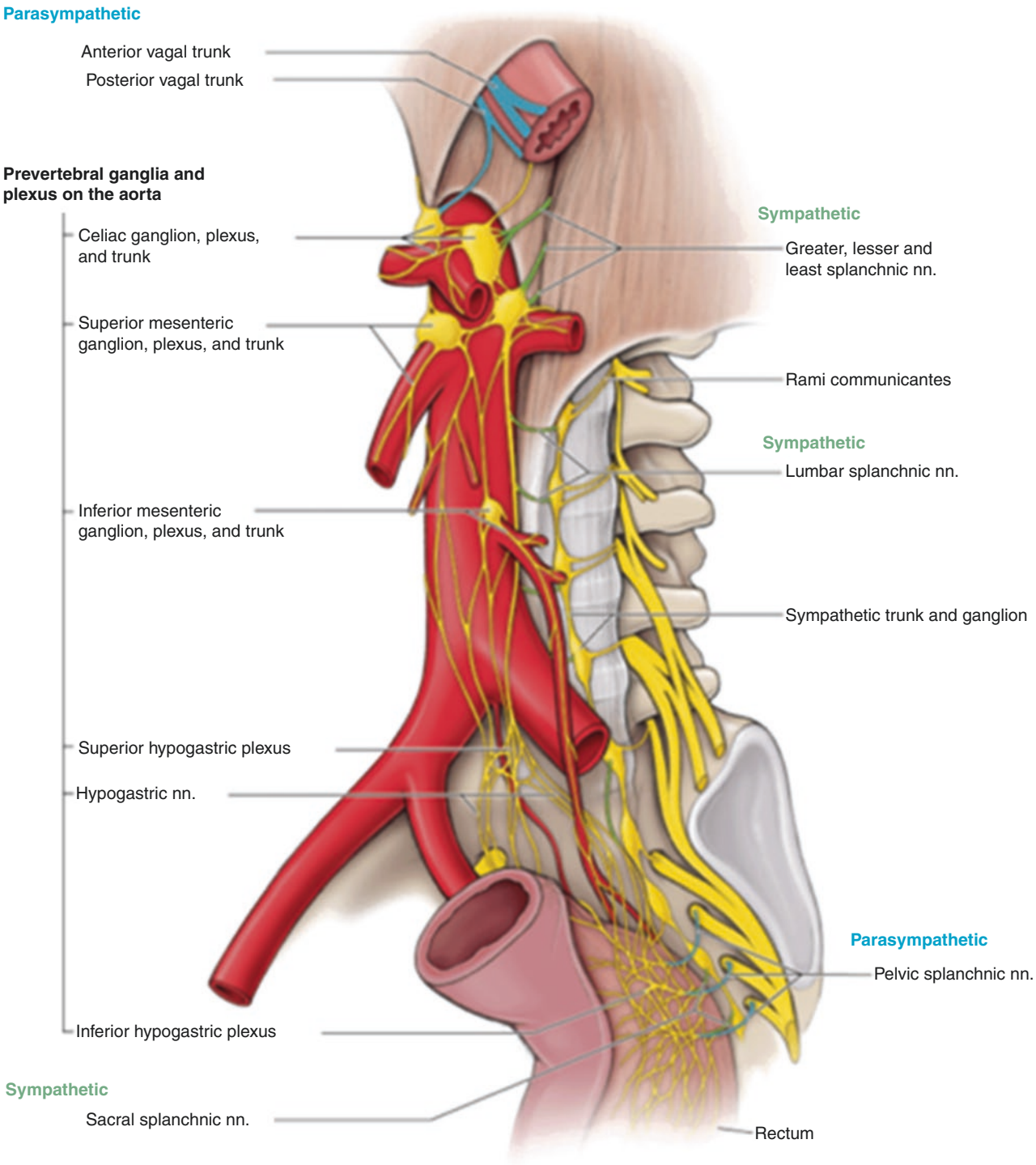

Fig. 68.1 The pelvic innervation. From The big picture: gross anatomy. McGraw Hill 2017

innervation to the bladder, ureter, seminal vesicles, prostate, rectum, and membranous urethra and somatic motor supply to the levator ani, coccygeus, and striated urethral sphincter [3].

The nerves to the prostate and corpora cavernosa cannot be directly visualized; however, their location can be inferred intraoperatively by identification of the neurovas-

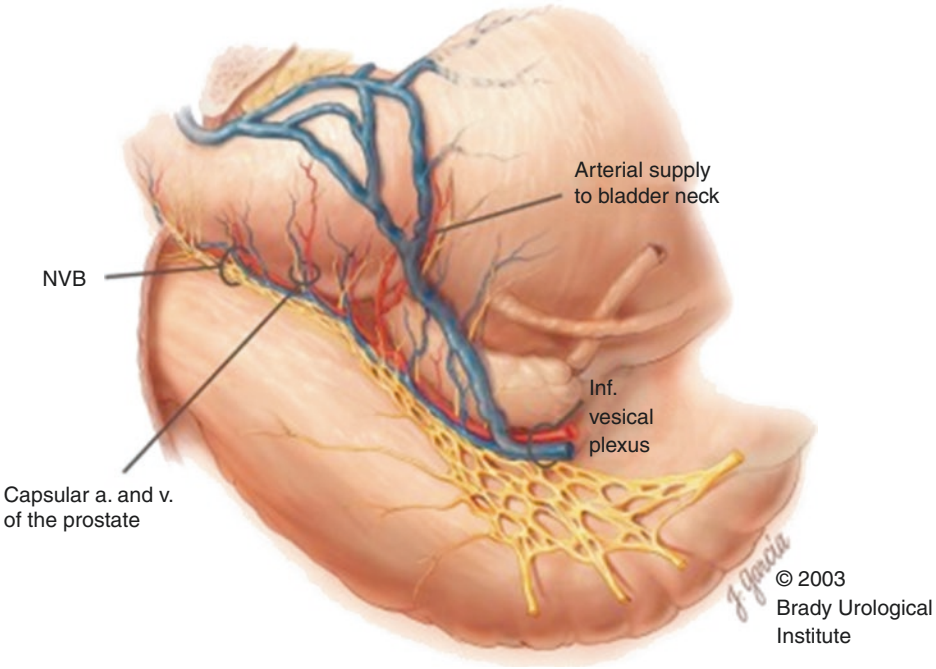

Fig. 68.2 The pelvic innervation in males. From Campbell-Walsh Urology. Chapter 114

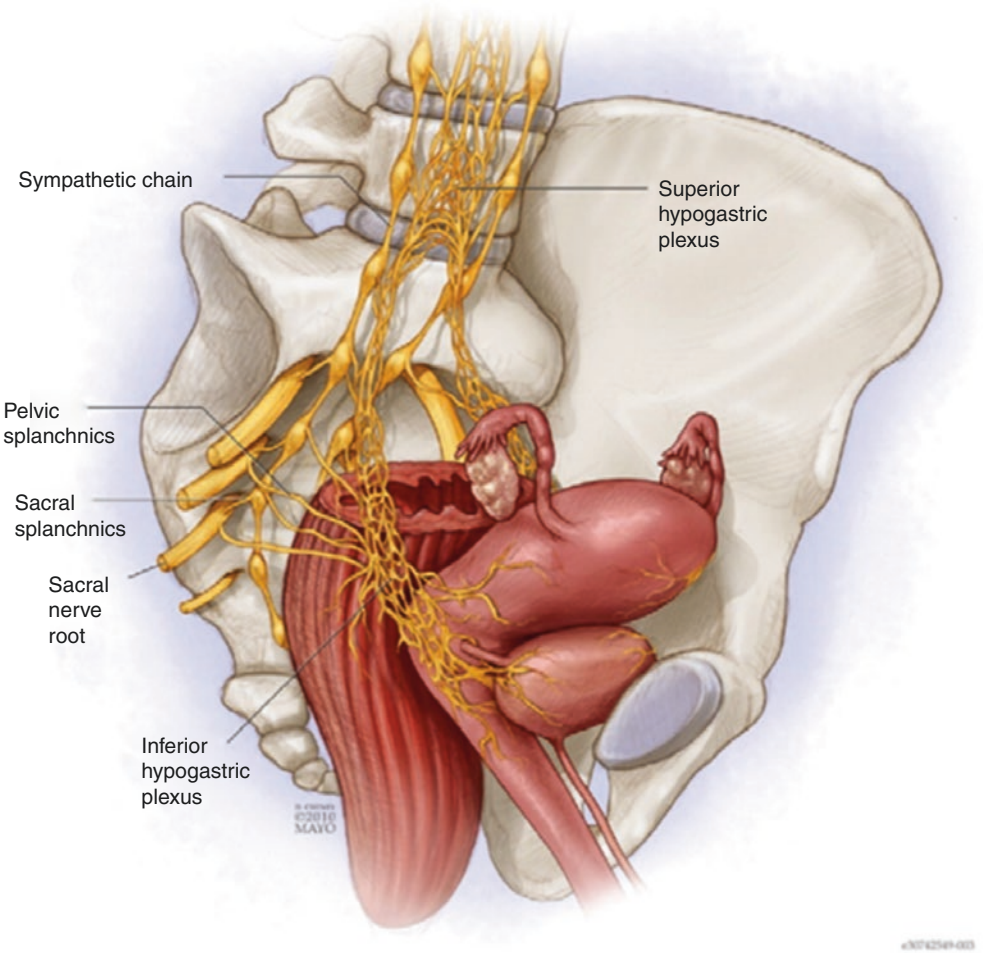

Fig. 68.3 The pelvic innervation in females. From Laterza et al., they cite Margina and Magtibay

cular bundle (NVB; Fig. 68.2) within which the nervous and vascular anatomy are intimately associated. The NVBs can be located in the lateral pelvic fascia between the prostatic fascia and the levator fascia [3].

Injuries to branches of the pudendal nerve can also occur and compromise somatic innervation of the external urethral sphincter. The pudendal nerve contributes somatic efferent branches from sacral roots 2–4 to the external urethral sphincter. Though anatomic variability exists, pudendal nerve branches to the EUS typically enter at the level of the prostatic urethra near the prostate apex or as retrograde branches from the dorsal nerve of the penis [9]. These branches may be injured during apical dissection or during stitching of the dorsal vein complex, respectively [9].

In females, the fibers of the inferior hypogastric plexus accompany branches of the internal iliac artery and are divided into three portions: the vesical, the uterovaginal (Frankenhauser's ganglion), and the middle rectal plexuses. The neurologic sequelae of radical hysterectomy are thought to result from disruption of the sympathetic and parasympathetic fibers supplying the urethra and bladder during ligation of the paracervical tissues [10]. However, there are multiple instances during radical hysterectomy which may result in autonomic denervation including: resection of uterosacral ligaments damaging the hypogastric nerves, resection of the dorsal paracervix and pararectal space damaging the inferior hypogastric plexus and the splanchnic nerves, resection of the lateral aspect of the paracervix inferior to the uterine vein damaging the inferior hypogastric plexus and splanchnic nerves, and finally with resection of the vesico-uterine ligaments damaging the distal portion of the inferior hypogastric plexus (Fig. 68.4) [11].

68.3 Symptoms

Since the autonomic nervous system facilitates normal bladder function, it is not surprising that damage during radical pelvic surgery can lead to dysfunctional voiding. Lower urinary tract dysfunction is the most common long term complication of radical surgery for cervical cancer, ranging from 8 to 80% [12–15]. The overall incidence of urodynamic bladder dysfunction after radical hysterectomy is 72% [14]. Among patients with post-hysterectomy lower urinary tract dysfunction, 42% is related to detrusor dysfunction with high or low compliance, 24.5% with mixed urinary incontinence, and 40% stress urinary incontinence (SUI) [9]. Studies with more than 1 year follow up have reported these disruptions in normal function may improve with resultant rates of 35%, 17%, and 38%, respectively [9]. Urodynamic studies have demonstrated that bladder compliance is decreased and post-void residual urine volume (PVR) is increased in both the short and long term after radical hysterectomy [9].

After radical pelvic surgery, the likelihood of SUI and voiding dysfunction is significantly increased [10]. The symptoms can be categorized as early and late dysfunction. Early findings include decreased bladder capacity, detrusor underactivity, and diminished bladder sensation resulting in voiding dysfunction. Delayed findings include voiding difficulty with abdominal straining, decreased bladder compliance, detrusor overactivity (DO), and urinary incontinence. These findings may resolve within 6 months to a year, or they may persist [16, 17].

68.4 Early Urodynamic Findings

Early lower urinary tract dysfunction (within 3–6 months) includes decreased bladder capacity, detrusor underactivity, and decreased bladder sensation often resulting in voiding dysfunction and in certain cases requiring intermittent catheterization [16, 17].

Chuang et al. [17] prospectively evaluated 24 consecutive women who underwent radical hysterectomy for cervical cancer stages Ia–IIa. Three patients were excluded due to preoperative SUI, and three patients were excluded due to

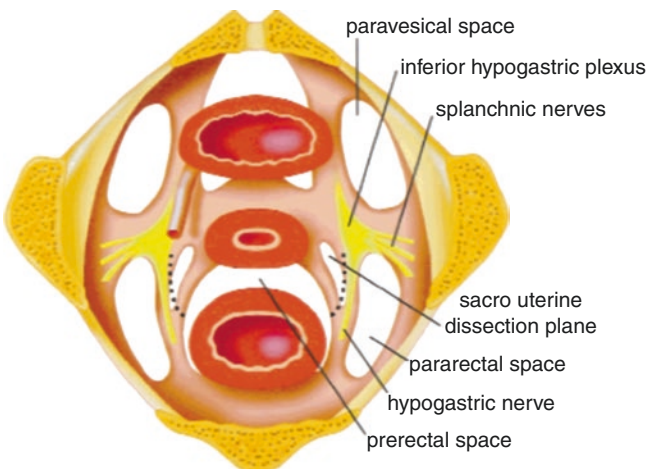

Fig. 68.4 The pelvic anatomy and innervation in females. From Laterza et al., they cite Ditto et al.

the diagnosis of diabetes mellitus resulting in 18 patients available for analysis. Urodynamic evaluations were performed preoperatively and at 2 weeks, 6 weeks, 3 months, and 6 months postoperatively. They noted significant reduction in bladder compliance and maximum urethral closure pressure (MUCP) at 3–6 months. Baseline MUCP decreased from 74 to 52 cm H_2O at 2 weeks and 53 cm H_2O at 6 months. Similarly, bladder compliance decreased from a baseline of 34–10 mL/cm H_2O at 2 weeks and 9 mL/cm H_2O at 3 months, but returned to 23 mL/cm H_2O by 6 months [18]. They also demonstrated that mean PVR increased from 113 mL preoperatively to 169 mL at 2 weeks ($p < 0.0001$) and 152 mL at 3 months ($p = 0.0003$); however, the residual volume returned to baseline by 6 months [17].

Uroflowmetry demonstrated a significant reduction in maximum flow rate (Qmax) at 2 weeks, 6 weeks, and 3 months after surgery with the most striking decrease at 2 weeks [17]. Preoperative Qmax decreased from a baseline of 10.9–3 mL/s at 2 weeks, but slowly trended back to baseline with values of 7.5 mL/s, 7.2 mL/s, and 14.4 mL/s at 2 weeks, 3 months, and 6 months, respectively [17]. This may be attributed to impaired parasympathetic motor innervation that disrupts detrusor contractility.

Kadono and colleagues performed urodynamics on 66 patients preoperatively, immediately after (3–4 days after catheter removal), and 1 year after robot assisted radical prostatectomy. They demonstrated significant decreases in bladder compliance (28.3–16.3 mL/cm H_2O) although this decrease did not persist 1 year following the procedure [19]. The mean detrusor pressure at maximum flow rate also decreased (from 61.9 to 34.3 cm H_2O) as did MUCP (from 84.2 to 33.4 cm H_2O); however, these differences persisted during urodynamics performed 1 year postoperatively. Intrinsic sphincter deficiency (ISD) by abdominal leak point pressure testing was observed in 53 (80.3%) patients even though no patient demonstrated ISD preoperatively [18].

In summary, although urodynamic parameters demonstrate significant changes immediately after radical pelvic surgery, many of these findings return to baseline between 6 months and 1 year. The following section seeks to evaluate long term findings during urodynamic testing.

68.5 Late Urodynamic Findings

Late urinary tract dysfunction usually reveals voiding difficulty with Valsalva augmentation, decreased bladder compliance, detrusor overactivity (DO), and SUI that may resolve or persist over time [16, 17]. Additionally, increased PVR delayed first voiding desire, and reduction of the maximum cystometric capacity have been observed [20].

Benedetti-Pancini et al. [19] retrospectively evaluated 76 women who underwent radical hysterectomy after neoadjuvant chemotherapy. The authors performed baseline urodynamics and urodynamics 1 year postoperatively. Twenty-six percent of patients reported urinary symptoms at 1 year follow up. Sensory loss was reported by 8%, difficulty initiating micturition was reported in 3%, and severe urinary incontinence was reported by 18% of patients [20]. Uroflowmetry demonstrated a significant decrease in peak flow (20.5–17.5 mL/s, $p < 0.01$) and flow time (27.7–48.3 s, $p < 0.01$) while also demonstrating a significant increase in PVR (24–96 mL, $p < 0.01$) [20]. Filling cystometry demonstrated an increase in first voiding desire (139–192 mL, $p < 0.01$) and concomitant decreases in maximum cystometric capacity (455–396 mL, $p < 0.01$), compliance (55.2–31 mL/cm H_2O, $p > 0.01$), and detrusor pressure at peak flow (31.9–27.6 cm H_2O, $p < 0.01$) [20].

A prospective case-control study of 32 women undergoing radical hysterectomy by Chen and colleagues demonstrated similar findings of decreased, though not statistically significant, bladder compliance (62.6–50.2 mL/cm H_2O, $p = 0.282$); however, they noted an increase in bladder capacity (296.6–347.6 mL, $p < 0.05$) during urodynamics 6 months postoperatively [16].

Chuang et al. [17] found that urethral pressure profiles demonstrated a significant decrease in MUCP from 68.6 to 58.7 cm H_2O [18]. Chen and colleagues confirmed these findings, noting a decrease of MUCP from 84.3 cm H_2O at baseline to 71.5 cm H_2O at 6 month follow up [17].

Song et al. [20] prospectively evaluated a cohort of men undergoing open radical prostatectomy with voiding questionnaires (ICS—male short form) and urodynamics. These metrics were performed preoperatively and at 3, 6, and 36 months postoperatively. They demonstrated significant decreases in maximum cystometric capacity (393–322 mL, $p < 0.001$), MUCP (63.7–53.2 cm H_2O, $p = 0.001$), and detrusor pressure at peak flow (54.1–45.3 cm H_2O, $p = 0.001$) at 3 years postoperatively [20]. They also demonstrated significant improvement in voiding symptom scores at 3 years; however, concomitant worsening in storage symptoms resulted in a net result of no change in health-related quality of life scores [20].

Kadono et al. [18] demonstrated that maximum cystometric capacity and bladder compliance were significantly decreased immediately postoperatively, but at 1 year both parameters returned to baseline values [18]. Detrusor pressure at peak flow was significantly lower both immediately and at 1 year postoperatively (61.9 cm H_2O, 34.3 cm H_2O, and 35.6 cm H_2O, respectively) [18]. MUCP was significantly decreased from baseline immediately postoperatively, and though values improved at 1 year postoperatively they were still significantly decreased from baseline (84.2 cm H_2O, 33.4 cm H_2O, and 63.0 cm H_2O, respectively) [18]. Interestingly, while abdominal leak point pressures were significantly below baseline immediately post procedure, they returned to baseline levels by 1 year (132.6 cm H_2O, 57.3 cm H_2O, and 128.5 cm H_2O, respectively) [18].

A review article published by Porena and colleagues sought to evaluate the available body of literature surrounding voiding dysfunction after radical retropubic prostatectomy. They identified ten prospective and nine retrospective studies; urodynamic parameters were required to be included in the review. Their review of the literature revealed contradictory data with regards to bladder filling sensation, cystometric bladder capacity, DO, and impaired contractility. A decrease in bladder compliance was noted in 8–39% of patients, and this was noted to have arisen de novo in 50% [21].

68.5.1 Detrusor Overactivity/Urinary Incontinence

Retrospective studies have shown that DO as an isolated urodynamic finding occurs in approximately 10% of men; however, DO most commonly presents along with other urodynamic abnormalities [22]. Huckabay and Constantinou have reported rates of post-prostatectomy urinary incontinence related to detrusor overactivity at 13% and 28%, respectively [23, 24].

Prospective studies fail to demonstrate consistent rates of de novo DO after radical retropubic prostatectomy. Kleinhans followed 44 men with a mean follow up of 7.6 months and demonstrated DO in only 6.8% of patients [25]. Conversely, Constantinou demonstrated DO rates of 62% in 13 patients with mean follow-up of 23 months, and Huckabay reported DO in 40% of 60 patients with mean follow-up of 32 months [23, 24].

With regard to postoperative urinary incontinence, Porena et al. report that ISD is the principal diagnosis in 55% of incontinent patients [21]. However, ISD is identified as the sole cause of incontinence in as few as 8% or as many as 71% of patients [23, 27–34]. The association of ISD with detrusor dysfunction is also quite variable, ranging from 0 to 88% [23, 26–36].

68.6 Conclusion

While many studies document early alterations in urodynamic parameters after radical pelvic surgery, long term evaluations demonstrate that many parameters return to baseline. Impaired compliance, decreased MUCP, increased PVR, and decreased Qmax seem to be consistent findings across multiple studies in the early postoperative period, however, many of these parameters will return to preoperative baseline. Though long-term decreases in compliance and MUCP after radical hysterectomy have been reliably demonstrated across multiple studies, conflicting data exist with regard to alterations in maximum cystometric capacity. Likewise, the data with regard to long term urodynamic alterations after radical prostatectomy are conflicting, though multiple studies suggest that a sustained decrease in MUCP and bladder compliance is expected.

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