Author query: (1) Plz provide citations in text for tables 29.1 to 29.4 and figures 29.1 and 29.2;
(2) Plz check the highlighted text for its accuracy

CHAPTER 29

An Approach to Children with Neurogenic Bladder Dysfunction

VT Haridas

Urinary bladder has a complex innervations with somatic and sympathetic systems and carries out dual functions of storage and emptying of urine. At least 25% of the clinical problems seen in pediatric urology are the result of neurologic lesions that affect the lower urinary tract function. Our increasing understanding of the neurophysiology of bladder coupled with advances in urodynamic techniques specifically designed for infants and young children have provided more accurate assessment of pediatric lower urinary tract disorders.

Neural control of bladder—sphincter unit in children is age dependant and hence much more variable and complex than those of adults. Of the various classifications of bladder dysfunctions the one proposed by International Children's Continence society in 1997 is well accepted.[1]

BASIC NEUROANATOMY AND PHYSIOLOGY

A thorough knowledge about the complex bladder innervations and regulation is essential

Table 29.1 Etiologic classification of bladder dysfunction

A.	Derangement of nervous control • Congenital malformations of CNS—Myelomeningocele, spina bifida occulta, caudal regression syndrome, tethered cord syndrome. • Developmental disturbances—Mental retardation, dysfunctional voiding, urge syndrome • Acquired conditions like—cerebral palsy, spinal cord trauma, transverse myelitis, multiple sclerosis, vascular malformations
B.	Disorders of detrusor and sphincteric muscle function • Congenital conditions like muscular dystrophy, neuronal dysplasia • Acquired conditions like chronic bladder distension, fibrosis of bladder wall
C.	Structural abnormalities • Congenital conditions like—bladder exstrophy, prune belly syndrome, epispadias, posterior urethral valve and other urethral anomalies • Acquired conditions—traumatic stricture or damage to sphincter or urethra
D.	Other unclassified conditions • Giggle incontinence • Hinmann's syndrome • Ochoa syndrome [urofacial syndrome]

to understand the pathophysiology of various conditions affecting the bladder.[2,3] Anatomically, the bladder is divided into a "body" or "dome" made of detrusor smooth muscle and the base, which includes the trigone and bladder neck that are intimately connected to the pelvic floor. The bladder outlet is controlled by two sphincters—the internal urethral (smooth muscle) sphincter in the bladder neck and proximal urethra and the external (striated muscle) sphincter of the membranous urethra. Lower urinary tract has sympathetic, parasympathetic as well as somatic nerve supply. The hypogastric nerve carries sympathetic fibers, the pelvic nerve carries the parasympathetic innervation, while the pudendal nerve carries the somatic innervations.

The sympathetic innervation to the lower urinary tract arises from the T11-L2 cord level, synapse in the inferior mesenteric and hypogastric plexuses and reaches bladder via the hypogastric nerves. The sympathetic stimulation release norepinephrine which acts through α-adrenergic receptors in the bladder neck and proximal urethra as well as β-adrenergic receptors in the bladder fundus. Alpha adrenergic stimulation closes the sphincter whereas the beta adrenergic stimulation inhibits and relaxes the detrusor muscles. The function of sympathetic innervations is to facilitate storage.

Parasympathetic supply arises from the detrusor nucleus at the S2–S4 cord level, passes through the pelvic nerves to cholinergic parasympathetic ganglia in the detrusor. Acetylcholine released by activation of these neurons produces detrusor contraction through M2 and M3 muscarinic receptor activation. Parasympathetic innervation

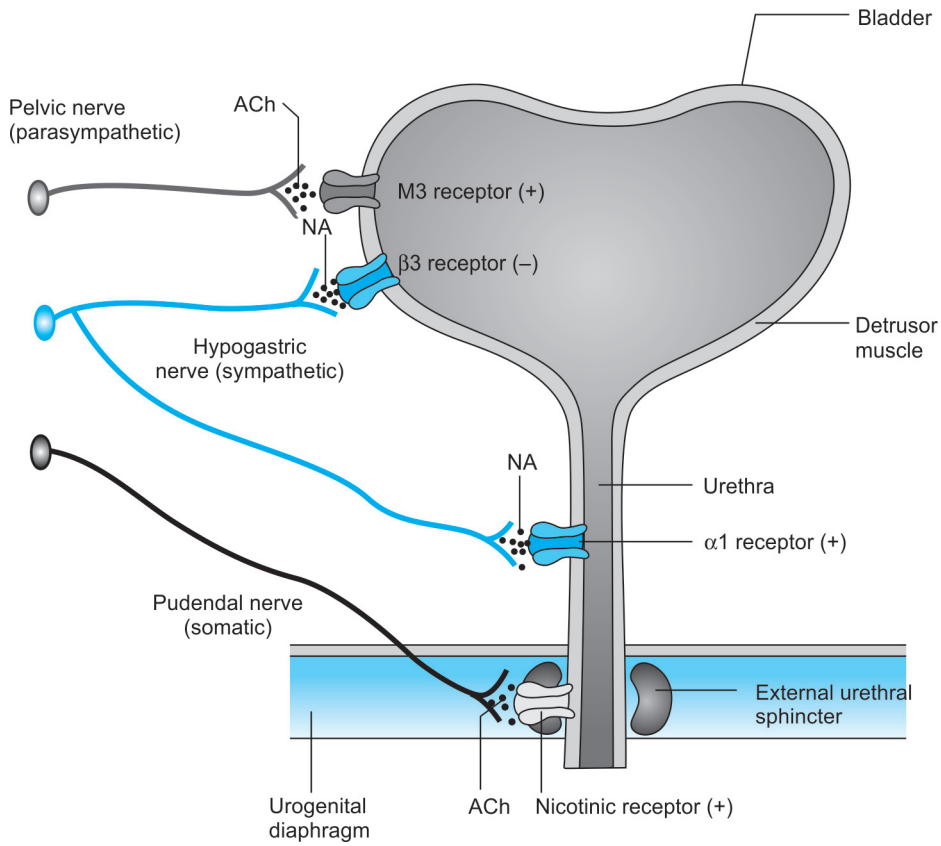

Figure 29.1 Innervation of lower urinary tract

in the proximal urethra causes nitric oxide to be released there which produces urethral smooth muscle relaxation. Parasympathetic stimulation thus results in detrusor contraction and relaxation of the proximal urethra. The parasympathetic supply is activated during micturition.

Somatic innervation to the external urethral sphincter arises from the pudendal (Onuf's) nucleus at the S2–S4 cord level and passes through the pudendal nerve to the striated sphincter muscle. Voluntary centers in the cerebral cortex exert excitatory influence on the pudendal nucleus to produce external urethral sphincter and pelvic floor contraction which maintains continence. When one decides to void voluntarily this influence is lifted to produce urethral and pelvic floor relaxation which facilitates bladder emptying.

A dense sensory supply of small myelinated Aδ fibers and unmyelinated C fibers is found in the suburothelial and muscular plexuses which relays information about the bladder filling. Free sensory fiber endings extend through the urothelium into the bladder cavity and acts as transducers of physical and chemical stimuli. The Aδ fibers respond to bladder wall distention and trigger micturition, while C fibers respond to painful stimuli. Afferent fibers are carried through the pelvic nerves, relayed through sacral dorsal root ganglia to the dorsal horn of the spinal cord. The sensory information about bladder filling and tension is further transmitted rostrally to the PAG region which is important in the control of micturition.

Micturition is a complex phenomenon controlled and co-ordinated by various centers in the spinal cord, brainstem, subcortical centers and cerebral cortex. Cortical control areas in the supplementary motor area and cingulate gyri as well as subcortical areas provide inhibitory influence on micturition at the level of the pons and excitatory influence on the external urinary sphincter. This allows voluntary control of micturition so that normally bladder evacuation can be delayed until an appropriate time and place to void are chosen.

The pontine micturition center (PMC, also known as Barrington's nucleus or M-region) is essential for the coordination of micturition. PMC modulates the opposing effects of the parasympathetic and sympathetic nervous systems on the lower urinary tract. PMC sends excitatory influence to the sacral spinal cord that produces detrusor contraction during emptying phase. Simultaneously thoracolumbar sympathetic outflow is inhibited producing internal urinary sphincter relaxation.[4] During bladder storage phase, PMC inhibits the sacral parasympathetic outflow leading to detrusor relaxation and simultaneously send excitatory influence to the thoracolumbar sympathetic centers producing internal urethral sphincter contraction. Experiments in lower animals have shown the presence of a group of neurons situated lateral to the PMC which inhibits voiding. This center is called L–region or lateral storage center. It is probable that such a center exists in human beings as well, but may not be anatomically well demarcated.

The PMC is under the direct excitatory influence of a group of neurons lying in the peri aqueductal gray matter (PAG). PAG receives ascending sensory information from the bladder afferents. Higher centers in the hypothalamus, thalamus, the anterior cingulate cortex, insula, and prefrontal cortex has immense connections with PAG. They influence PMC indirectly through PAG. On voluntarily initiating micturition, the prefrontal cortex inhibition of the PAG is lifted and simultaneously the hypothalamus stimulates the PAG. The overall result is excitation of the PMC which produces voiding.

During the filling phase, the parasympathetic innervation of the detrusor is inhibited and the smooth and striated parts of the urethral sphincter are activated, thus preventing leakage of urine. This is a spinal reflex known as the 'guarding reflex'. The afferent impulses arise from the urethra and bladder wall and spinal interneurons in the sacral cord plays an important role. Some input from pontine storage center might facilitate sphincter reflexes. Supraspinal centers produce inhibition of the pontine micturition center, which results in enhancement of thoracolumbar sympathetic outflow with simultaneous suppression of sacral parasympathetic outflow to the lower urinary tract. These supraspinal centers also produce excitatory outflow through the pudendal nerve to produce external urethral sphincter contraction. The overall

effect in normal bladder physiology is detrusor smooth muscle relaxation, bladder neck smooth muscle contraction, and external urinary sphincter skeletal muscle contraction that allow low pressure storage of urine in the bladder without leakage.

During the bladder emptying phase, the supraspinal centers' inhibitory outflow to the pontine micturition center is suppressed, resulting in reduction of thoracic sympathetic outflow with simultaneous enhancement of sacral parasympathetic outflow to the lower urinary tract.[4] The supraspinal centers' excitatory outflow through the pudendal nerve is suppressed producing external urethral sphincter relaxation. The overall effect in normal bladder physiology is detrusor smooth muscle contraction, bladder neck smooth muscle relaxation, and external urinary sphincter skeletal muscle relaxation that allow evacuation of urine stored in the bladder. The coordination between a contracting detrusor and a relaxing sphincter is lost in neurologic lesions especially those between the PMC and sacral cord. This detrusor sphincter dyssynergia can lead to obstruction in voiding and very high intravesical pressure leading to vesicoureteric reflux.

Maturation of Bladder Control

At birth, bladder is uninhibited and functions through reflex activities. Over the next 5–6 years the bladder control matures to the adult level.

Pathophysiology of Neurogenic Bladder

Many classifications have been used to group neurogenic bladder dysfunction. Each has their merits and clinical utility. These classifications may be based on urodynamic findings,[5,6] neurourologic criteria[7,8] or on bladder and urethral function.[9,10]

A popular classification of neurogenic bladder dysfunction based on the location of the neurologic lesions in the neural pathways is given below:

1. Lesions above the pontine micturition center (e.g. cerebral palsy, brain tumor, pediatric stroke) producing an uninhibited bladder. The bladder empties when full even in socially inappropriate time. The voiding is complete and there is no residual urine.
2. Lesions between the pontine micturition center and sacral spinal cord (e.g. Thoraco lumbar spina bifida, traumatic spinal cord injury) producing an upper motor neuron bladder also called an automatic bladder. Voluntary control is lost, the bladder volume is low and there is a high incidence of detrusor sphincter dyssynergia and reflux uropathy.
3. Sacral cord lesions that damage the detrusor nucleus but spare the pudendal nucleus producing a mixed type A bladder. Leads to a hypotonic bladder with large residual urine volume.
4. Sacral cord lesions that spare the detrusor nucleus but damage the pudendal nucleus producing a mixed type B bladder, results in incontinence.
5. Lower motor neuron bladder: Due to extensive damage of sacral cord or sacral nerve root injuries leading to an autonomic bladder. The bladder is totally denervated, is hypotonic and incontinent.

EVALUATION

The evaluation of a child with a neurogenic bladder includes a careful history of bladder and bowel habits, a thorough physical examination followed by relevant investigations. Symptoms due to lower urinary tract dysfunction may be broadly classified into storage symptoms and voiding symptoms. A

Table 29.2 Bladder control at various ages

At birth	*Spinal reflex*	*Spontaneous, uninhibited micturition*
1–2 years	Frontal and parietal centers mature, bladder capacity increase	Bladder sensation appreciated, but micturition is still voluntary
3–4 years	Attains voluntary control of external sphincter when awake	Can postpone voiding
4–5 years	Cortical inhibition attained	Dry by night
More than 6 years	Can initiate micturition even if bladder is not full	Can initiate micturition in socially acceptable circumstances

careful history of bowel habits is equally important and must address the frequency of defecation and presence of fecal incontinence.

Abdomen should be palpated for a distended bladder or a loaded colon. A genitourinary examination should be done to look for developmental anomalies and dermatologic signs of urinary incontinence. The back should be examined for any congenital anomalies of the spine as well as any midline cutaneous markers such as dimples, hemangioma, nevus, or isolated tuft of hair. Asymmetry of the gluteal cleft may suggest abnormal sacral development. The anus is examined for sphincter tone and any evidence of fissures, skin tags, or hemorrhoids.

Investigations include urinalysis for infections, renal parameters to look for renal dysfunction, radiologic evaluation and urodynamic study.[11] An ultra sound examination of the abdomen and pelvis can easily detect developmental anomalies, signs of obstructive uropathy like hydronephrosis and post void residual urine.

URODYNAMIC STUDY OF BLADDER

Urodynamic studies (UDS) have revolutionized the assessment and management of pediatric neurogenic bladder in the last two decades.UDS is helpful in detecting, quantifying and in assessing the response to treatment. A computerized UDS lab carries out the tests as given in **Table 29.4**.

Bladder capacity in children above one year can be calculated using the Koff's formula- Bladder capacity [mL] = [Age [years] + 2] × 30. A normal bladder has good compliance and fills up to 200–300 mL without much increase in the pressure. Detrusor starts contracting after a particular level. The normal filling pressure should be <10 cm H_2O while the normal voiding pressure varies from 55 cm to 80 cm H_2O in boys and from 30 cm to 65 cm H_2O in girls. Detrusor over activity is considered an abnormal finding at any time. The examination findings are considered normal when there is an appropriate capacity, good compliant bladder, with no overactivity and normal innervation of

Table 29.3 Common symptoms of neurogenic bladder dysfunction

Symptoms due to abnormal filling	*Voiding symptoms*
• Increased day time frequency • Increased nocturnal frequency • Urgency • Urge incontinence • Stress incontinence • Mixed urgency and stress incontinence • Nocturnal enuresis • Continuous urinary incontinence • Situational incontinence – giggle • Abnormal bladder sensation—increased, decreased, absent	• Hesitancy • Straining • Slow stream • Splitting or spraying • Intermittent stream • Terminal dribble • Post micturition dribble • Incomplete emptying

Table 29.4 Common tests used in urodynamics

- *Cystometry* helps to assess the bladder capacity, detrusor pressure, compliance, and bladder sensation
- *Uroflowmetry* evaluates the volume and flow rate of urine and helps in analyzing symptoms like hesitancy and intermittency
- *Residual urine volume* can be assessed using a post void USG or postvoid catheterization
- *Urethral pressure profile* studies the changes in urethral pressure during rest, micturition as well as maneuvers like cough and Valsalva's maneuver. Useful in analyzing incontinence as well as outlet obstruction
- *Pressure-flow micturition studies*
- *Video-urodynamic studies* simultaneous video recording using a radio-contrast dye and fluoroscopy helps in visually assessing detrusor contraction, vesicoureteral reflux and detrusor sphincter dyssynergia
- *Electrophysiologic studies* include sphincter EMG, pudendal nerve conduction study, pudendal somato sensory evoked potential [SSEP]—useful in assessing the integrity of local neural pathways

the sphincter with normal sacral reflexes and an increase in sphincter activity during filling and complete silencing during emptying. An upper motor neuron lesion is present when there is detrusor overactivity, a failure of the sphincter muscle to relax with a bladder contraction or leaking of bladder during filling. A lower motor neuron lesion is noted when there are no contractions of the detrusor muscle, denervation in sphincter EMG, no response in the sphincter to sacral reflexes during filling and voiding.

Urodynamic Study Based Functional Classification

With the advent of urodynamics it has become easier to assess the function of bladder during storage as well as voiding phase. Even subclinical abnormalities can be easily picked up, quantified and can be followed up. This has led to more practical classification of neurogenic bladder. The urodynamic study based classification accepted by International Continence Society (ICS) as well as the Madersbacher classification[12] accepted by European Association Urology (EAU) are gaining popularity. These classifications also help in planning therapy as the functional abnormalities are simplified down to practical problems like overe ctive or underactive detrusor, overactive or underactive urethra during storing or voiding phase.

Overactive bladder can be managed by having a fluid intake schedule aiming for 1000–1200 mL urine out put per day and drugs to reduce the detrusor contractions. Commonly used drugs are anticholinergics and tricyclic antidepressants. Non selective anticholinergic agents like oxybutinin and selective agents like darifenacin or

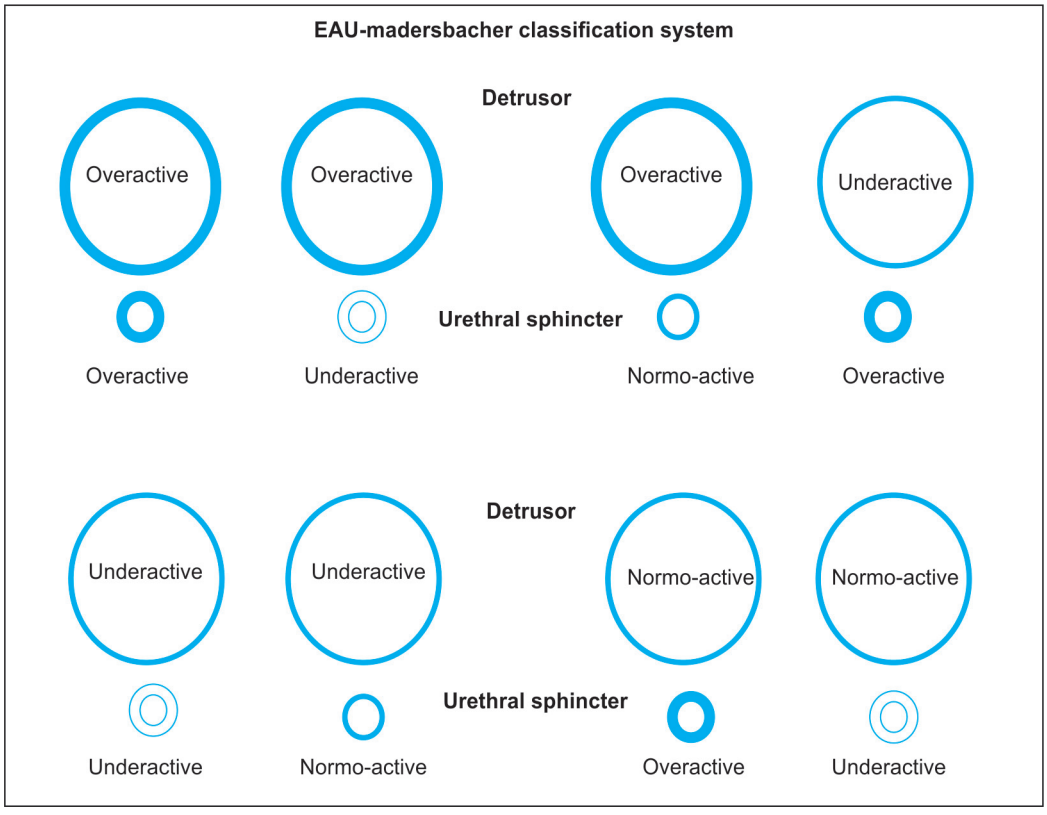

Figure 29.2 European association urology (EAU) classification of neurogenic bladder

solifenacin have been found to be useful. Tricyclic antidepressants like imipramine and amitriptyline have anti-cholinergic action on the detrusor muscles as well as alpha adrenergic action at the bladder neck and internal sphincter.[13] Injection of botulinum toxin in the detrusor muscles produces transient chemodenervation and reduce detrs or overactivity lasting for 3–8 months.[14] Intravesical capsaicin instillation to reduce the hyperactivity of deafferented C fibers, sacral neuromodulation and augmentation of bladder capacity using by cystoplasty are reserved for resistant cases of overactive bladder.

Alpha 1 receptor antagonists like terazosin, alfuzosin and doxazosin are used to reduce the high tone of a spastic sphincter. Benzodiazepines and baclofen which act through GABA-ergic inhibition have also been found to be useful. Botox injection to sphincter, sphincterotomy and urethral stents are reserved for those patients who fail to respond to pharamacological manipulation.

Drugs like duloxetine and pelvic floor exercises are found to be beneficial only in a minor subset of children with lax sphincter. Sling procedures may help these subjects to attain continence. Bladder neck closure and urinary diversion to colon has to be considered if the incontinence is intractable. Sacral cord stimulation and artificial urinary sphincter are emerging as promising therapeutic modalities for intractable incontinence.

Underactive bladder is of large volume and usually has high residual urine leading to recurrent UTI. Therapy with cholinergic drugs like bethanechol does not yield any significant clinical benefits. Clean intermittent catheterization (CIC) may be resorted to in these patients.

The concept of CIC introduced by lapides[15] four decades back has made a tremendous impact in the efficient management of complex neurogenic bladder dysfunction. The patient or caregiver is taught to catheterize the bladder 4–6 times a day. It is not a strictly aseptic procedure and hence the term 'clean'. Even though the subsequent urinalysis reveal significant bacterial colonization, clinically significant UTI are rare. CIC mimics the normal bladder physiology of storage phase for hours and intermittent voiding. CIC has been found useful to tackle complex problems like high detrusor pressure and reflux uropathy, recurrent UTI due to residual urine, bladder decompensation due to over distension, detrusor sphincter dyssynergia and spastic nonrelaxing sphincter.

COMMON PEDIATRIC NEUROUROLOGIC CONDITIONS

Bladder Dysfunction in Cerebral Palsy

More than one third of children with cerebral palsy present with dysfunctional urinary symptoms. Common symptoms include stress incontinence, frequency, urgency and difficulty in initiating micturition. Children with CP develops bladder control later than their normal counterparts. Cognitive abilities and IQ also can influence the attainment of bladder control. Neurogenic detrusor overactivity is observed in 70% of children with CP. As a result the functional bladder capacity is reduced and uninhibited contractions may result in incontinence. Detrusor sphincter dyssynergia is very rare in CP as the Pontine center and its connection with the spinal centers are intact.

Bladder Dysfunction in Spina Bifida

Incidence of spina bifida worldwide ranges from 0.3–4.5 per 1000 live births. Renal damage is an important cause for mortality and starts as early as the sixth month. The principal aims in the management of urological problems in spina bifida are:

- Preservation of renal function
- Achieve urinary dryness by school age
- Independence at an older age with respect to bowel and bladder care
- Maintain sexual and reproductive functions.

Presence of an overactive bladder and detrusor sphincter dyssynergia (DSD) increases the risk of renal failure and hence the assessment should be aimed to detect them at the earliest. Anal sphincter tone should be checked during the initial examination. A tightly closed anal sphincter may indicate an overactive pelvic floor and indirectly the possibility of DSD. The first UDS may be delayed till the second month, especially in children undergoing surgery in the neonatal period, as the pelvic floor behavior may change postoperatively.

All new born patients with spina bifida and suspected high bladder pressure are put on clean intermittent catheterization along with anticholinergics like oxybutinin to reduce the bladder activity and UTI prophylaxis with agents like trimethoprim. CIC is carried out initially by the care givers and subsequently by the child him/herself by the age of 8–9 years. CIC done properly at least 3 times a day has reduced the need for bladder augmentation surgery from 90% to less than 5%. The child is followed up yearly with UDS to look for bladder activity, capacity and compliance as well as USG to look for upper tract dilatation and renal development. If the bladder capacity is normal for age and the end filling detrusor pressure is less than 30 mL H_2O, the child may be followed up with regular CIC and anticholinergics. If the detrusor filling pressure is more than 40 cm H_2O and the voiding pressure is more than 100 cm H_2O and capacity is low surgical augmentation using ileocystoplasty or colocystoplasty may be considered.

Spina bifida patients with paralyzed pelvic floor are incontinent. Their detrusor pressure will be low, hence upper tract injury due to reflux is rare. Children need bladder neck surgery to attain continence. Transvaginal sling procedure in girls and transabdominal puboprostatic sling procedur in boys are the standard surgeries. Persistent leakage after sling surgeries can be tackled by injecting urethral bulking agents like silicon.

The timing for surgical procedure is determined by the type of bladder abnormality and magnitude. A surgical procedure may have to be performed even as early as by the third month of life in children with serious threat to the upper urinary tract.

Children with occult spinal dysraphism and sacral agenesis should undergo a MRI study of the spine as well as a UDS with sphincter EMG to assess the extent and nature of lesion. Almost equal incidence of upper and lower motor neuron lesions [35% vs 40%] are observed in these subjects.

Bladder Dysfunction in Acquired Myelopathies

Spinal cord injuries, demyelinating diseases like pediatric multiple sclerosis, vascular insults and infective myelitis are the main acquired myelopathies causing neurogenic bladder. The presence of severe motor deficits and disabilities often distracts the clinicians attention from the urologic dysfunction. Recurrent urinary infections and renal damage are the chief causes for morbidity and mortality in these unfortunate children and they should be addressed and managed during the acute stage itself.

Hinman's Syndrome

Also known as non-neurogenic neurogenic bladder is an acquired condition characterized by bladder—sphincter dyssynergia and poor emptying leading to decompensation and recurrent UTI. Urodynamic study shows a pattern classical of neurogenic bladder. Various mechanisms including occult spinal dysraphism, acquired psychological abnormality leading to voluntary sphincter disturbance and isolated bladder neuropathy have all been proposed. The management strategy is the same as for any other neurogenic bladder.

Nocturnal Enuresis

Primary nocturnal enuresis, a very common clinical problem in pediatric urology, usually results from a non-neurogenic dysfunction. Close observation and analysis have revealed that these children have multiple pathophysiologic mechanisms and hence need varying treatment strategies. A subset of these subjects have abnormally low Anti-Diuretic Hormone (ADH) secretion at night and will respond only to ADH replacement. Low bladder capacity and compliance, uninhibited bladder contractions, elevated arousal threshold leading to "heavy sleep" and psychological stress have all been found to play significant roles in the causation.

CONCLUSION

Neurogenic bladder dysfunction in children may result from congenital malformations like spina bifida as well as due to multiple acquired conditions like trauma and demyelinating diseases. Irrespective of the etiology, the basic principle in the management is to achieve a compliant bladder

with adequate volume and low filling pressure which can empty intermittently. Judicious use of medications, techniques like CIC and surgical procedures can ensure a healthy upper urinary tract, longer life span and psycho-social well being.

BIBLIOGRAPHY

1. Abrams P, Blaivas JG, Stanton SL, et al. Standardisation of terminology of lower urinary tract function. Neurourology and Urodynamics. 1988;7(5):403-27.
2. Bors E, Comarr AE. Neurological Urology. Baltimore, MD, USA: University Park Press; 1971.
3. Dorsher PT, McIntosh PM. Neurogenic bladder. Adv Urol. 2012;2012:816274. doi: 10.1155/2012/816274.
4. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008;9:453-66.
5. Fowler CJ, O'Malley KJ. Investigation and management of neurogenic bladder dysfunction. J Neurol Neurosurg Psychiatry 2003;74(Suppl 4):iv27-31.
6. Hald T, Bradley WE. The Urinary Bladder: Neurology and Dynamics. Baltimore, MD, USA: Williams and Wilkins; 1982.
7. Krane RJ, Siroky MB. Classification of neuro-urologic disorders. In: Krane RJ, Siroky MB (Eds). Clinical Neuro-Urology. Boston, Mass, USA: Little Brown; 1979.pp.143-58.
8. Lapides J, Diokno AC, Silber SJ, Lowe BS. "Clean, intermittent self-catheterization in the treatment of urinary tract disease," Journal of Urology. 1972;107(3):458-61.
9. Lapides J. Neuromuscular vesical and urethral dysfunction. In: Campbell MF, Harrison JH. Urology. Philadelphia, PA, USA: WB Saunders; 1997.pp.1343-79.
10. Madersbacher HG. Neurogenic bladder dysfunction. Curr Opin Urol. 1999;9(4):303-7.
11. Norgaard JP, van Gool JD, Hjalmas K, et al. Standardization and definitions in lower urinary tract dysfunction in children. International Children's Continence Society. Br J Urol. 1998;81 [suppl 3):1-16.
12. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005;174:196200.
13. Wein AJ. "Lower urinary tract dysfunction in neurologic injury and disease," In Campbell-Walsh Urology, Wein AJ, Kavoussi L, Novick AC, Partin AW, Peters CA (Eds). Saunders, New York, NY, USA, 9th edition, 2007.pp.2011-45.
14. Wein AJ. Classification of voiding dysfunction: a simple approach. In: Barrett DM, Wein AJ, (Eds). Controversies in Neuro-Urology. New York, NY, USA: Churchill Livingstone; 1984.
15. Yamaguchi O, Nishizawa O, Takeda M, et al. "Clinical guidelines for overactive bladder: guidelines," International Journal of Urology. 2009;16(2):126-42.