Modern Management of Neurogenic Bladder: Making the Child the Focus of Therapeutic Efforts

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Abstract: The management of children with neurogenic bladder (NB) has remained a source of great dilemma for paediatric urologists since time immemorial. Several paths have been approached to reach the ultimate goal of upper tract preservation as well as to grant a socially acceptable life to these children and their families. Over the years, the 'proactive' approach of universal institution of therapy from the neonatal period onwards has gradually taken precedence over a 'reactive' approach, based on urodynamic parameters or the radiological sequelae. In this review we have summarized the various available options in the management of neurogenic bladder.

Key words: Detrusor instability, Neurogenic bladder, Urodynamic parameters

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Introduction

The management of children with neurogenic bladder (NB) has remained a source of great dilemma for paediatric urologists since time immemorial. Several paths have been approached to reach the ultimate goal of upper tract preservation as well as to grant a socially acceptable life to these children and their families. Over the years, the 'proactive' approach of universal institution of therapy from the neonatal period onwards has gradually taken precedence over a 'reactive' approach, based on urodynamic parameters or the radiological sequelae.

Of the neuropathic and non-neuropathic causes of NB, spinal dysraphism is the most common aetiology, with myelomeningocele (MMC) leading with 80% incidence. Other causes are uncommon in children including acquired cases occurring as a consequence of traumatic, oncologic or vascular pathology of the spinal cord, supraspinal and peripheral lesions and the non-neuropathic lesions.

Conventionally, the etiology of the neuropathic bladder is divided into the following categories: central, peripheral or mixed. But this classification has very little role to play in therapeutic decision-making. Management is dictated by the basic state of the bladder after the neurological event:

- Detrusor overactivity with sphincter overactivity
- Detrusor inactivity with sphincter overactivity
- Detrusor overactivity with sphincter inactivity
- Detrusor inactivity with sphincter inactivity

A particular child tends to stick to the same category over the course of time owing to the unchanged primary pathology. Of the four categories, 'detrusor underactivity and sphincter underactivity' is inherently 'safe' in that, if untreated, the upper tracts remain preserved whereas 'detrusor overactivity with sphincter overactivity' which, when diagnosed, should sound alarm bells immediately lest the upper tracts get affected.

Given the 20% incidence of death due to renal damage during the first year of life and the invariably dismal outcome of the disease, management should start as soon as a diagnosis is made. For the individual patient, therapy is a lifelong requisite. Management starts with explaining the family about the cause, prognosis and ultimate goals of treatment so as to sensitize them adequately to get out of the 'shame and blame' game and accept the child and the problem.

Time is of essence regardless of the strategic approach instituted. The urologic sequelae of this condition are quite morbid. The apparent discrepancy between the treatment end-
points of a doctor and a parent must be clarified before initiating treatment. The care-givers should realise that the doctor prioritizes the preservation of the upper tracts, while the doctor should realise that the social stigma of an incontinent child is nerve-wracking for any parent.

**Approach to A Child with Neurogenic Bladder**

Accurate evaluation and characterization of the neurological status of the lower urinary tract form the bedrock of treatment. This begins with a careful history of bladder and bowel habits. This includes questions to assess LUTS (lower urinary tract symptomatology) such as urinary frequency, urgency, intermittency, and incontinence or any history of UTIs. It is also necessary to assess whether the bladder evacuates completely after each void or if the child is simply overflowing urine from a chronically full bladder. A careful history of bowel habits is equally important and must address the frequency of defecation and the character of stool. The correlation of bladder and bowel dysfunction remains an enigma with some suggesting a local phenomenon due to rectal distension and others postulating a role of the interaction between the locus ceruleus and the pontine micturition centre.\(^5\)

The physical exam should include a careful abdominal examination, palpating for any masses, such as due to fecoliths or retained urine. A careful genitourinary examination should confirm normal anatomy, as well as check for the presence of ammoniacal dermatitis. The back is checked for any anomalies of the spine as well as any midline skin lesions, such as a hemangioma, nevus, isolated tuft of hair, or dimples. One should also note the presence and symmetry of the gluteal cleft. The anus is examined for sphincter tone and the integrity of the local reflex arcs.

**Table 1. Observed complications with testicular prosthesis**

<table>
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<th>Neurourinary Bladder Management Goals</th>
<th>Hemorrhoid Bladder Management Goals</th>
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The assessment continues with a radiologic evaluation and urodynamic study. The initial assessment must include a renal ultrasound (with a note of the amount of postvoid residual urine), voiding cystourethrogram (VCUG) to assess bladder capacity, shape and presence of vesicoureteric reflux (VUR), and an urodynamic study. NB should be suspected in any child with a long history of micturition disturbances or during diagnostic work-up for other symptoms e.g. severe constipation or psychological disorders with encopresis. It is very important not to label every child with voiding issues as a patient with a “neurogenic” bladder to avoid over-diagnosis and stigmatization. An algorithm for the basic tenets of management are summarised as a flow chart:-

**Intrauterine Intervention**

Fetal surgery for antenatally diagnosed neural tube defects has been pondered over and even attempted several times but no definite conclusions have been drawn. Clayton *et al* in 2011 studied the long term outcomes of fetal MMC surgery and demonstrated a range of urological dysfunctions in this subset including decreased bladder capacity, detrusor overactivity, and increased detrusor pressure with no significant difference compared with individuals who underwent traditional postnatal repair.\(^6\)

MOMS trial (management of MMC study)\(^7\) was a prospective, multicentre, randomised controlled trial established by the National Institutes of Health in 2003 to evaluate the results of intrauterine surgery in the United States. The end-points evaluated were:

1. Fetal and infant mortality
2. Need for a ventriculoperitoneal shunt at the age of 1 year
3. Mental and motor development at 30 months age

The rates for shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group. The prenatal surgery group had better motor function compared with the postnatal surgery group. The trial was prematurely terminated because the overall data limited efficacy of prenatal surgery. A retrospective analysis of the data from this trial will evaluate the urologic outcomes.\(^7\)

Fetal surgery is still nascent and thus, an attempt must be made to prevent damage at the time of the primary repair. Neurophysiological monitoring may be used to assist the surgeon with intraoperative planning and prevent iatrogenic worsening of urological function.\(^8\) Tarcan reported on 56 patients with secondary tethering after repair of MMC and evaluated outcomes after a detethering procedure. They evaluated the outcomes according to the initial grade of urinary tract dilation. Individuals with Grade 1-2 dilation had an improvement in grade in 40% of the cases and complete resolution of the dilation in 33.3%. Those with Grade 3-4 dilation had an improvement in 50% of the cases and resolution in none.

The surgeon should be aware of the possibility of re-tethering during follow-up and consider early detethering to give such bladders another chance to improve.

**Non-surgical Modalities**

Before surgery is considered, conservative protocols have to be maximized because two-thirds of patients can become continent by clean intermittent catheterization (CIC) and medication alone.\(^9\) Urodynamic studies have a major role to play in diagnosing and following these children since they forebode the urologist of the deleterious effects of a high pressure system rather than looking at the effects on the upper and lower tracts per se radiologically. McGuire and colleagues noted that 80% of patients with intravesical pressures greater than 40cm H20 at urinary leakage (detrusor leak point pressure [DLPP]) had reflux and/or hydronephrosis.\(^10\) Beyond this pressure, upper tract damage occurs in 70% of the children.\(^11\)

**Pharmacological Agents**

The aim of pharmacotherapy in neurogenic bladders is to bring about one or more of the following effects-decrease detrusor overactivity, increase bladder capacity, and/or increase bladder outlet resistance.

The drug oxybutynin hydrochloride has brought a paradigm shift in the outlook of patients with NB and is the most studied.\(^12,13\) The anti-cholinergic action against the M3 muscarinic receptors on the wall of detrusor muscle relaxes it and thereby decreases intravesical pressures and uninhibited contractions and also indirectly increases bladder capacity. It also has an anti-spasmodic, local anaesthetic and calcium channel blocking properties which augment its effect on the overactive detrusor and “pharmacologically convert” it into an inactive reservoir.\(^14\) It is administered orally in the dose of 0.2-0.4 mg/kg/day in 2-3 divided doses. The dose has to be limited sometimes in view of the side effects of altered thermoregulation and constipation. Alternatives also exist, such as transdermal patches and intravesical instillation (tablets are dissolved in water and instilled directly into the bladder by catheterization). It was demonstrated that a reduced first-pass metabolism of oxybutynin after intravesical instillation, resulting in a reduced generation of the N-desethyl metabolite, may explain the clinically relevant reduction of systemic side effects that characterizes intravesical compared with oral oxybutynin therapy.\(^15\)

Other bladder relaxant drugs include propiverine (0.8mg/kg/day), trospium, and tolterodine. The current experience with compounds other than oxybutynin is still limited in children with NB. Propiverine hydrochloride, with its anti-muscarinic
Empties the bladder adequately without leaving any residual urine and hence no risk of infection

Keeps the upper tracts safe of reflux prior to high pressure voiding

Valuable tool to keep the child dry

Efforts to perform a sterile technique each time have not shown a significant difference in the incidence of UTI, although long-term randomized studies are limited. Starting CIC will frequently result in chronic colonization of the bladder by bacteria. These bacteria are generally of low clinical consequence to urinary tract health if they are evacuated on a regular basis. Cloudy or foul-smelling urine is a common phenomenon of the chronically colonized bladder, but does not necessitate antibiotic treatment. Antibiotic use should be reserved only for a symptomatic episode of UTI. Overuse of antibiotics will contribute to formation of antibiotic-resistant organisms. The urine culture should be checked periodically for the presence of certain urease-positive organisms, such as Pseudomonas and Proteus, which need treatment to minimize formation of urinary tract stones or biofilms.

A useful adjunct to a program of intermittent catheterization is a watch that is scheduled to alarm on a regular basis every 3-4 hours to help remind the child to catheterize on a timed schedule and not based on their urge to urinate. A major problem with doing CIC from an artificially created stoma is the risk of urine being left and consequently leading to infection, hence the tube inserted should be left to drain into a bowl kept at a lower level (on the floor) for complete evacuation. Spontaneous reflux resolution was recorded in 43% to 58% of cases with standard conservative treatment with a combination of CIC, anticholinergics and prophylactic antibiotics.

Clean Intermittent Catheterization (CIC)

Lapides et al in the 1970s introduced CIC as a simple, effective way of keeping the bladder empty and thereby preventing the reflux of urine in case of high intravesical pressures. Assuming fewer than 10% of children with congenital NB will develop satisfactory bladder control without need for CIC, all parents are initially counselled and reminded at periodic follow-ups to expect this intervention by the age of toilet training if urodynamic evaluation does not indicate earlier management.

Some authors prefer early institution of CIC in all infants with NB, given the fact that by the age of 3 years, CIC will be required in all for achieving continence, and given the difficulties of starting CIC in toddlers. Such early institution of CIC seems to improve the compliance of caregivers and their ability to assist the child in coping with his/her condition. CIC can be done by parents till the child achieves sufficient dexterity to do it on his own, usually by around 7-8 years of age. CIC done at regular intervals has several advantages:

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Another facet of pharmacotherapy is the use of prophylactic antibiotic cover in these children. However, the downside of daily antibiotics is the risk of developing antibiotic-resistant organisms. Low dose, low efficacy antibiotics such as co-trimoxazole and nitrofurantoin should be used in an alternative fashion for prophylaxis and replaced by high-efficacy full dose drugs for an active infection.

New drug development is taking place at a rapid pace. Bladder specific calcium channel openers, intravesical vanilloid (resiniferatoxin) treatment, tachykinin antagonists and calcium mobilizing and calcium signal modulating agents are all being studied as potential pharmacotherapeutic agents in NB.

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Intradermator Botox Toxin (BOTOTOX) Injection

Persistent high pressure or uninhibited contractions (UIC)
are treated by increasing oral oxybutynin to tolerance and/or adding intravesical instillation of 5 mg two to three times daily as needed. In unusual cases with continued UI, Botox injection is recommended. BOTOX results in decreased muscle activity by blocking the release of acetylcholine from the neuron by preventing the vesicle where the acetylcholine is stored from binding to the membrane where the neurotransmitter can be released. This effectively weakens the muscle for a period of three to four months. This ultimately projects as an increase in bladder capacity, decreased pressures, decreased incidence of reflux and improves continence.

A recent systematic review (six studies) encompassing 108 children (mean age 9.8 years) with neurogenic detrusor overactivity managed with CIC who were treated with BOTOX injection were evaluated from 2002 to 2006. Follow-up was reported at 4 to 12 week intervals up to 26 weeks. BOTOX injection resulted in a mean 40-80% reduction from baseline, and 65-87% of children became completely continent between catheterizations. All six studies showed a significant reduction in maximum detrusor pressure and corresponded with an increase in maximum cystometric capacity (percentage increase from baseline ranging from 35-80%). Clinical efficacy was noted within 2 weeks from injection and these benefits were noted to persist for 3 to 6 months.

**Bowel Management**

One cannot effectively manage this disorder without careful attention to neurogenic bowel management. The degree of fecal incontinence is unpredictable and depends on the extent of the neuropathy and the effectiveness of the anal sphincter action. The large volume of hard stool retained in the colon occupies space in the pelvis and places pressure on the bladder that compromises the ability to store and evacuate urine effectively. It is useful to consider strategies of scheduled evacuation. This includes healthy dietary fiber intake and a daily stool softener, coupled with a method of daily evacuation to achieve effective bowel management. Biofeedback programmes have not been shown to be more effective in achieving fecal continence than a bowel management programme.

**Surgical Modalities**

**To Increase Bladder Storage Capacity**

The ideal state of the bladder with minimum long term effects on the upper and lower tracts is the presence of low pressure storage and physiologic storage pressure at an adequate volume. The volume at which pressure increase occurs is defined as the "reflex volume." It is intuitive that a high reflex volume will aid in the protection of the upper tracts. A number of surgical options are available should a combination of pharmacotherapy and CIC prove inadequate in halting the progression of urinary tract damage. It is imperative that one must have an unscarred bladder to work with and a mechanism of satisfactory bladder emptying.

As mentioned previously, a more conservative approach to improving the storage capacity of the detrusor is by the intramural Botox injection. Failing this, one may think of "partial autoaugmentation" with the use of detrusor myectomy. The urothelium is left intact and post-procedure urinary decompression by regular CIC is mandatory while the anatomic and physiologic reconstruction takes place (usually in the next 1-2 years). The use of additional tissue to cover the muscular defect does not contribute significantly to outcomes.

Bladder augmentation is usually kept low on the list of surgical options due to the complexity and inherent long-term morbidity of these procedures. Enterocystoplasty and clam cystoplasty are good alternatives when the surgeon is faced with a small, scarred bladder. Clam cystoplasty involves the insertion of a patch of intestine on the longitudinally opened posterior wall of the bladder. Despite the simple elegance of autoaugmentation, it has not proved as useful as the use of intestinal segments to increase storage capacity. The choice of surgery leans towards urinary diversion in the form of continent or incontinent urinary diversion and bladder reconstruction/replacement in the event of intractable incontinence, diminishing renal functions and hypertension following long-term renal damage.

**Neuromodulation**

Neuromodulation therapy aims to treat the abnormal innervation of the bladder, trying to "re-train" the nerve-muscle interaction to attain more normal bladder function. The available treatments include nonsurgical therapies, such as transurethral electrical bladder stimulation; minimally invasive procedures, such as implantation of a sacral neuromodulation pacemaker device; and operative procedures that reconfigure sacral nerve root anatomy. Sacral neuromodulation by a reversible implantable device (InterStim, Medtronic, Minneapolis, MN, USA), is thought to improve bladder function either by consistent stimulation of the efferent fibers of the sacral nerve roots or by providing rhythmic contractions of the pelvic floor. Hagerty, Richards and Kaplan were the main proponent of the technique of transurethral electrical bladder stimulation in children and reported a series of 372 patients with a mean age of 5.5 years and mean follow-up 6.6 years. In 76.9% of these patients, the increase in bladder capacity was 20% or greater.

Another method of counteracting a small, hyperactive bladder that is available for patients with high and complete cord lesions is the intradural transection of the S2-S4 nerve roots which in effect achieves deafferentation of the urinary bladder.
A necessary pre-requisite is that the bladder should be compliant and the person must possess enough manual dexterity and means to achieve regular intermittent self-catheterization. As most of the patients in whom this modality is chosen have a high cord lesion, the latter criterion may not be fulfilled. In such cases, sacral electrostimulation (e.g. Brindley stimulator) can be utilized to initiate voluntary voiding, defaecation and even penile erections.

Sauerwein et al\textsuperscript{47} and Kutzenberger et al\textsuperscript{48} noted a less than satisfactory effect of these implants in erectile dysfunction in this group of patients. Addressing this along with the myriad psychosexual issues that develop as a natural consequence is important as eventually our paediatric patients grow into adolescence and adulthood due to the longer survival times. Guys et al\textsuperscript{49} described the results of sacral nerve stimulation (SNS) therapy in children with neurogenic bladder dysfunction. They studied the results in 42 children with neurogenic bladder dysfunction, mainly due to spina bifida. Twenty-one children were randomized between the conservative and interventional arms. This group did not find significantly better results in the SNS group and postulated that it could be due to a small study group or very severe bladder function.

**Surgery for the Incompetent Bladder Outlet**

**Bladder Neck Bulking Agents**

In case of sphincter underactivity/pelvic floor paresis, bladder neck procedures are the way to achieve continence. Agents that have been employed for urethral injection include autologous fat, polytetrafluoroethylene, bovine collagen, and pyrolytic carbon-coated zirconium oxide beads (Durasphere). Bulking agents also include silicon grains in povidone (MACROPLASTIQUE) injected by suprapubic puncture under transurethral endoscopic vision control. In the current era, Deflux is being used as a bulking agent in the region of bladder neck.

In a series of patients with mixed causes of incontinence and mean follow-up of 28 months, bladder neck injection using dextranomer/hyaluronic acid polymer (Deflux) resulted in a dry interval of 4 hours in 48% of 27 children with neuropathic bladders, 4 of whom underwent failed treatment with slings.\textsuperscript{50} Similarly, polydimethylsiloxane injection ended pad use in 34% of 44 children with NBs, 24 of whom underwent prior bladder neck procedures, at median follow-up of 28 months.\textsuperscript{51} The main disadvantage with this approach is the difficulty in CIC which follows.

Neel et al\textsuperscript{52} have introduced the concept of total endoscopic management (TEM) in children with noncompliant NB to address continence and treatment of VUR. Ten children with NB (mean age 5.9 years) who did not respond to maximal anticholinergic dosing and CIC were treated with cystoscopic injection of botulinum-A toxin in the detrusor and subureteric injection of Deflux. At 1 month, a significant increase in bladder capacity (79±49 to 155±55 ml), increase in bladder compliance (from 1.4 to 4.3 ml/cmH2O), and decrease in maximum detrusor pressure (from 55±16 to 37±11 cmH2O) were noted. These improvements were maintained at 6-months follow-up. VUR was successfully treated in 15 of 16 ureters (94%). Five of six incontinent patients achieved complete dryness. This study provides an interesting approach to avoid bladder augmentation in this population.

**Bladder Neck Slings and Bladder Neck Reconstruction**

One of the more enduring questions when choosing these techniques is whether to carry out concomitant bladder augmentation. Male children have a potential for prostatic growth and thus may be served by bladder augmentation alone despite low outlet resistance.\textsuperscript{53}

Kreder et al\textsuperscript{54} advocated that supporting the bladder neck with a sling may be enough to abolish leakage if the preoperative urodynamic assessment, performed with some form of bladder outlet occlusion, shows a stable bladder with sufficient capacity and normal compliance. Whatever the choice based on pre-operative radiological studies and urodynamics, the durability of the sling and longevity of the procedure must be foremost in the surgeon’s mind when applied to the paediatric population.

**Artificial Urinary Sphincter (AUS)**

American Medical Systems currently produced the AMS 800 model which is the only AUS currently available in the market. The three components include a cuff which fits around the urethra or bladder neck; a balloon fluid reservoir which is implanted in the abdomen; and a pump which is implanted in the scrotum or labia to control activation. The device can be activated a few weeks after surgery by squeezing the bulb of the pump which forces fluid into the hollow cuff which occludes the urethra. Prior to voiding, the bulb is pumped to push fluid back into the reservoir. Care must be taken during cystourethrocopic visualization.

There is a controversy regarding the ideal time for implantation of the AUS in the paediatric age group. Both Kryger et al\textsuperscript{55} and Levesque et al\textsuperscript{56} found no increase in the rate of AUS re-insertion with growth. Kryger et al also found no difference in the continence rate, revision rate, augmentation rate, or number of complications in patients who received an AUS before age 11 compared to those placed later in life. AUS insertion, in fact, may be easier in prepubertal patients secondary to the shallower pelvis and lesser degree of periurethral venous plexus engorgement. Revisions for retraction of the pump in the scrotum were uncommon, occurring only in 1 of their 25 patients.\textsuperscript{55}
Conclusion

What should and can be achieved is a more or less adequate, low-pressure, functional capacity of the bladder that is emptied as completely as possible. Newer techniques are being pioneered at an astonishing rate and the modern surgeon has a smorgasbord of techniques to choose from and can "custom-fit" the therapy to his/her patient. Tissue engineering will play an increasing role in the future with the first reports of the use of this ground-breaking technique reported by Atala et al in 2006. It is an alternative to the free grafts that are conventionally used and is grown by seeding autologous cells harvested from the bladder onto a scaffold of "extracellular matrix".

The ultimate goals though are to provide continence, to prevent bladder-wall destruction, and to preserve upper tract function. It is not always possible to reach these objectives. Therefore, one should keep in mind some basic rules. First, renal function preservation is more important than continence. Second, noninvasive measures take priority over surgery, as the former are reversible but the latter is not. Ultimately, the treating physician has to realise the primacy of the individual in the holistic view of management. The 'child' is the focus-not the 'disease'.

References


