*Anand Sinha, MS, MCh and Minu Bajpai, MS, MCh, PhD, FRCS, FNAMS, National Board, Fulbright Scholar**

Neurogenic Bladder: Long Term Consequences

**Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi 110029, India*

The primary aim of treatment in neurogenic bladders is attaining a significant dry period and preventing renal damage. There is no permanent cure to the condition per se and the treatment is life-long. The matters are made worse as the disease sets in as early as the neonatal period, leaving the child exposed to an entire lifetime of treatment. Even well treated children may have a scarred psychosocial development. More than a quarter of all the severe lower urinary tract anomalies in children can be attributed to neurogenic causes and myelodysplasia is the commonest cause of neuropathic bladder in childhood.[1] More than 90% of patients with myelomeningocele have some degree of lower urinary tract dysfunction depending on the level and extent of the neurological injury.[2] Neuropathic bladder dysfunction is also found in children with anorectal agenesis secondary to associated spinal anomalies and sometimes due to pelvic surgery. Other causes of neurogenic bladder include acquired spinal cord lesions like trauma and neoplasms.[3]

Renal failure and incontinence are the most frequent urological problems in patients with myelodysplasia. In the past, most children with myelodysplasia succumbed to complications from hydrocephalus and renal failure.[4] Those who survived till adulthood had an eight fold risk of renal failure as compared to the normal population. With improved care and routine surveillance more patients are now surviving longer and reach adolescence and adulthood.[5]

The Adolescent with Neurogenic Bladder

It is important to closely monitor adolescents with significant neurological abnormalities as physical growth can unmask decompensated states.[6] The neurological and intellectual development in incomplete till adolescence and hence are children in their teens are not goal-oriented, are rebellious, engage in risky behaviours and do not prioritize their own health. Beyond adolescence individuals develop target orientation, significant relationships and sexual function. Incontinence that presents or persists into adolescence has a negative impact on the self-esteem and mental health and interferes with the process of achieving independence. It is also at this stage that adolescents develop an understanding of their disease and they should be properly explained regarding the nature of the disease, its natural course and the importance of adherence to the therapy. Adolescence is an emotionally turbulent phase of life and patients can be significantly scarred due to incontinence, continuous smell of urine and tedious therapies.

Overall passage to adolescence is kind to the bladder that has no overt disease.[6] However children with diseased bladders, the general tendency is to worsen as aging produces muscle and nerve degeneration in the bladder wall. Almost all children with a neuropathic bladder will have received treatment of the bladder aimed at preserving the kidneys and maintaining continence. Treatment has been aimed at reducing the storage pressure to less than 40 cm water and maintaining continence by clean intermittent catheterization (CIC), anticholinergic drugs and, when necessary, bladder augmentation.[7] Patients who have been managed optimally in childhood reach adolescence with a normal upper urinary tract, fair bladder compliance and capacity, self-emptying at acceptable intervals, and continence between catheterizations.[8] With proper management in childhood adolescent patients are able to independently take care of themselves with CICs and bowel movements. With properly opted modalities, the patients get rid of urinary tract infections and dilated upper tracts.

Wider application of urodynamic testing in the evaluation of infants and young children with neurogenic bladders has led to the better pathophysiological understanding of the natural history of bladders in patients with spina bifida.[9] About 35% of bladders worsen in infancy and one third of children who develop impaired kidney drainage do so within the first year of life. Studies reveal progressive deterioration by the age of 3 years in up to 58% of patients on serial urodynamic testing.[9] Thereafter, urodynamic characteristics of the bladder usually reach a plateau. A late change in bladder behaviour usually indicates a change in the neurological status and is an absolute indication for a neurological opinion.[10]

Although there has been no formal study, there is a distinct clinical impression that bladder and renal function deteriorates (Fig. 1a and Fig. 1b) at puberty,[11] especially in the presence of high grade reflux, female gender and when CIC was started at an older age.[12] Various factors may be responsible for the same. In few patients this can

be attributed to cord tethering, although as this is almost a universal finding in spina bifida and deterioration with growth does not always occur and there must be other explanations. Another factor responsible is the development of increased bladder outlet obstruction, presumably from growth of the prostate and estrogenization of the urethra in females. An adolescent who recently develops long dry periods suddenly around puberty, is usually due to an increased leak point pressure and are at high risk of developing renal failure. Renal deterioration is also be accelerated by the presence of high grade vesicoureteral reflux. Early institution of clean intermittent catheterization (CIC) can limit this problem but it still occurs. Other factors which pose a threat at puberty are bladder wall thickening and poor compliance which may cause ureteral obstruction.[11] So it is essential that bladder management be organized in childhood. The ideal is a low pressure reservoir, if necessary achieved with augmentation, and continence with clean intermittent catheterization.

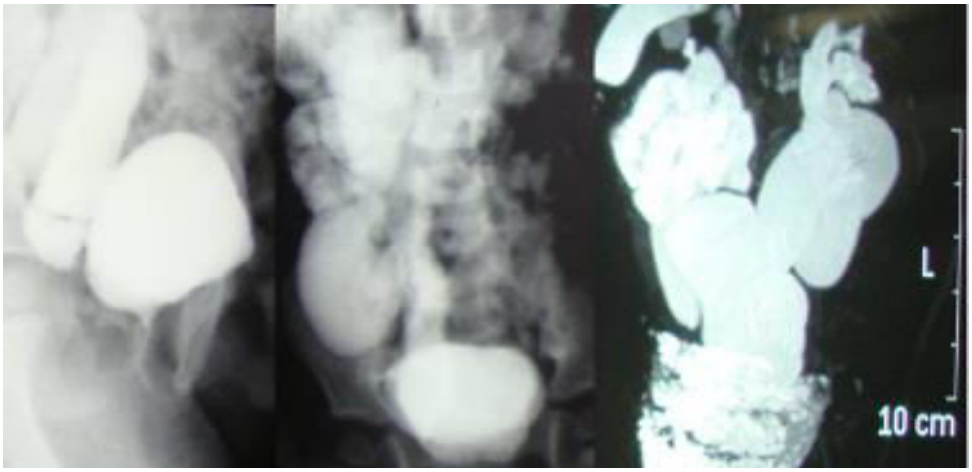

Fig. 1a.Bilateral severe upper tract dilatation persisting in an adolescent with neurogenic bladder; not adequately treated in childhood

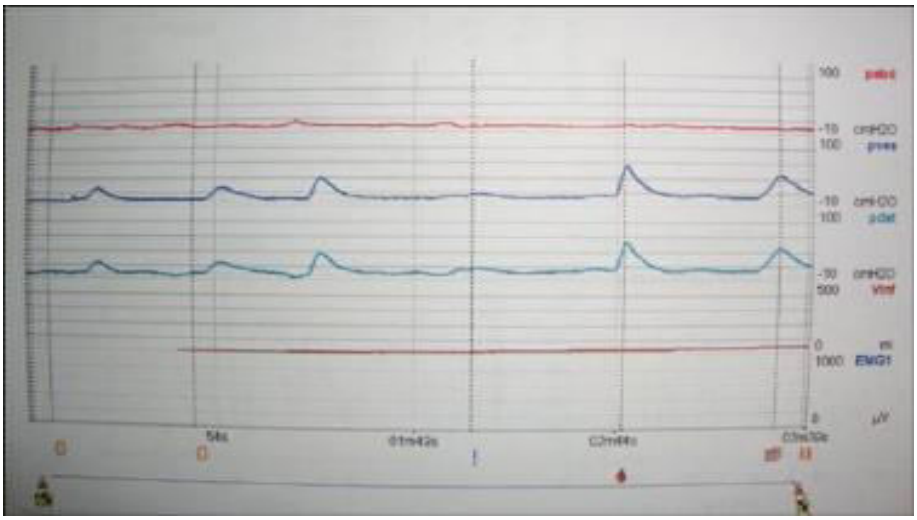

Fig. 1b.Urodynamics of the same patient showing high pressure bladder with poor compliance and multiple uninhibited detrusor contractions. (Age=12 years; Expected capacity=420ml; Maximal cystometric capacity=146ml; Leak point pressure=43cm H2O)

Surveillance of Adolescents with Neurogenic Bladder

Close surveillance is of utmost importance for patients for neurogenic bladder. As already emphasized the bladder can deteriorate with age especially around puberty. If not monitored, such children can land up with

renal failure even before they show worsening in their symptoms. Till the renal function is stabilised and the management is well taught to the patients, frequent visits and regular pertinent investigations are necessary. The primary aim should be preservation of renal function. Bladder needs to be rehabilitated to an extent where it does not transit high pressures to the upper tracts and facilitates adequate ureteral clearance. If done properly it should be possible for a child to enter adulthood with non dilated upper tracts. Both medical and surgical measures should be utilised to optimum to gain the primary objective. Good renal function promises adequate growth and survival of the patient. It is important to ensure complete bladder emptying and prevent recurrent urinary tract infections (UTIs). Reflux is secondary in patients with neuropathic bladders and can be dealt with only if bladder is adequately reared. Results of surgical and medical measures to treat reflux are dismal if the bladders persist with high end filling pressures. Augmentation cystoplasty should be considered for refractory bladders. Augmentation may be the only effective way to deal with persistent reflux in such patients. Achieving social continence is also essential. It is the most important biofeedback for patients and it is the only way to ensure patient compliance towards such a tedious treatment.

Till the above goals are met, the monitoring is tailor-made for each individual patient. However once the patient is stabilised with a particular treatment schedule, monitoring should be optimized. Unnecessary frequent visits dampen the parents and patients sense of well being. But at the same time infrequent and inadequate follow-up may result in worsening renal function and it may be too late before detection. Close monitoring throughout the transition from child to adulthood allows detection of signs of deterioration of the urinary tract at an early stage and facilitates prompt intervention to halt damage and preserve kidney function.[13] Long term surveillance should be based on the following guidelines.

1. It is essential to timely recognise symptoms of developing dysfunction. Any change in the signs and symptoms should be noted promptly and the patients should be encouraged to bring it to the treating physicians notice promptly. Adolescents tend to ignore their symptoms out of rebel or fear of embarrassment. It is essential therefore that they are encouraged to come forward with any fresh onset of symptoms, poor adherence to medication, and catheterization regimens.
2. Thorough enquiry should be made regarding adherence to made to medication and catheterization regimes. Treatment in neuropathic bladders is troublesome and non compliance may arise due to a number of factors. Lapses are common when patients take over the responsibility of their own catheterization regimes and dosing. Parents need to be motivated to remain involved in this transition till they ensure that the child pursues the regimes diligently. Cost is a very important factor especially in the developing nations. Anticholinergic medications and catheters and related equipment may pose a significant financial burden on the family. It is important firstly to impregnate the importance of the therapy in the minds of the family and the patient. Secondly support groups should be established to help out such families financially and emotionally. It is even more difficult to ensure adherence to therapy in under-educated families and female patients.
3. Recently acquired changes in signs and symptoms need to be investigated optimally. Where possible tests should be minimally invasive and only performed after clear explanations about the rationale and consequences of abnormal findings.[13] Unnecessary tests add to the cost to the family and society and can even prove hazardous if the tests are invasive.
4. Sensitivity to sexuality is important when investigating adolescent patients. Even individuals performing intermittent self-catheterization can be embarrassed during intimate testing.[13] It is preferable for the patients to be examined by physicians of the same gender and by the same physician every visit.
5. Various tests also pose a threat of radiation. Since these children require life-long therapy it is essential to minimise the risk of radiation and such investigations should be ordered with caution and only if absolutely essential. At the same time one should not deter from rationally investigating a child when it is the need of the hour.
6. Pregnancy should be excluded prior to radiologic imaging or an anaesthetic procedure, and the reason why should be explained properly.
7. Normal kidney growth and any deviations can be monitored non-invasively by serial ultrasonography. Other costly investigations like renal dynamic and cortical scans can be justified only if ultrasonography reveals a suspicion of worsening dilation, parenchymal scarring or atrophy or recurrent febrile UTI. Ultrasounds can also detect increased bladder wall thickness, impaired bladder emptying, dilated lower ureters, or frank hydronephrosis.
8. Psychological evaluation is also essential for these patients. Persistent dribbling, soiled clothes, urinary smell and associated fecal incontinence greatly deter a person's self esteem. An empathetic attitude and

wherever required psychotherapy should to adapted. Support groups and encouraging patients to talk with similar patients also helps the moral of these individuals.

9. A balance must be achieved between realistic follow-up that does cramp to the patient's life style, but frequent enough to detect threatening changes in the function of the urinary tract. It is difficult to impose an exact interval for follow- up, but annual review, seems reasonable (Table 1).[14] Flexibility in scheduling may be needed to maintain patient adherence.

TABLE 1. Surveillance protocol for neurogenic bladder patients

Investigation	Frequency
Visit	Yearly and if symptomatic
Ultrasound	
Serum Creatinine	
Glomerular Filtration Rate (GFR)	
Renal dynamic scans	Indications
Renal cortical scan	1. Symptoms (i) Flank pain (ii) Recurrent UTI 1. Ultrasound (i) Worsened hydroureteronephrosis (ii) Cortical thinning 1. Fall in GFR
Urodynamic study	Indications 1. Yearly till child grows and dose of drugs need to be altered with weight (14-16 years) 2. Symptoms (i) Flank pain (ii) Recurrent UTI 1. Ultrasound (i) Worsened hydroureteronephrosis (ii) Cortical thinning 1. Fall in GFR
Micturating cystourethrogram	Recurrent UTI Previously unresolved high grade refluxes Very high capacity low pressure bladders

Lawrenson *et al*[14] conducted a study between 1994 and 1997 to quantify the risk of renal failure in patients of neurogenic bladder. The prevalence and incidence of renal failure and renal replacement therapy in the general population was ascertained, as was the prevalence of multiple sclerosis, paraplegia and neural tube defects. The prevalence of renal failure in each of the special populations was then compared with the prevalence in the unaffected general population. The rate ratio of renal failure compared with the general population in each of the years 1994-1997 for neural tube defects ranged between males 6.8-9.0 and females 9.2-11.5. As expected, people with neural tube defects were found to have a substantially increased risk of renal failure compared with the general population. This study recommended that all patients should be regularly screened so that renal impairment may be detected prior to the development of renal failure. It also emphasized on the higher risk found in females.

The Impact of Clean Intermittent Catheterization (CIC) on Quality of Life

The concept of clean intermittent catheterization was introduced by Lapides in 1972. After introduction of clean intermittent catheterization Diockno *et al* published their first long term follow up of ten years in 1983.[15] They found that less than half of their initial 60 patients were still performing catheterization. However, this apparently poor result was largely accounted for by 25% who were lost to follow-up, dead or had a change in

neurological status of the original group only 10 were children with myelomeningocele who would have grown into adulthood, and it is implied that the majority of these were still performing clean intermittent catheterization. The lack of other follow-up may reflect a general clinical satisfaction with catheterization for basic management. But still it is important to provide a suitable environment to the individual to properly practice CIC.

It is essential to properly train the patients to do CICs themselves as it is integral to such patients developing a sense of independence and allows them to move away from caregivers without restrictions. Children should be able to perform CIC for themselves from the age of 6 to 9 years. In males it is imperative to prevent urethral strictures and false passage. Catheters should be well lubricated and should be inserted without forceful manipulation. In females locating the urethra may be difficult especially in wheelchair bound females and the use of mirrors to do the same is advocated. Non reusable low-friction catheters are considered valuable in high-risk male patients with urethral false passage or very tense sphincters but are unnecessary in routine cases. In order to promote complete bladder emptying CIC should be performed with the largest catheter that can be passed and should be performed for optimum time durations. Finally, given the high prevalence of latex allergy, in the spina bifida population, a strict latex-free approach is of extreme importance.[13]

There were two schools of thoughts regarding the timing of initiation of CICs in patients with myelodysplasia. With long term follow up studies, it has been proven beyond doubt that patients in whom CICs have been started empirically in the first year of life itself do far better than their compatriots in whom CIC was initiated on developing patients. It is far easier for the parents to institute CIC in the neonatal period than when they reached the toddler age. Infants on CICs tend to adopt CIC fairly conveniently later in life while the older children pose significant resistance to allowing themselves to be catheterized for the first time. In the long run, children with early empiric institution of CICs tend to have better bladder dynamics, renal function and better quality of life scores. Kaefer *et al* in 1999[8] published their results on the long term benefits of initiating CIC early. The authors retrospectively reviewed urological outcomes in patients with myelodysplasia who were at risk for urological deterioration within year 1 of life based on bladder sphincter dyssynergia and/or high filling or voiding pressure. They recorded the dates when high risk voiding dynamics were initially observed, and when intermittent catheterization and anticholinergic therapy were initiated. Patients in whom treatment began at the time a high risk profile was noted (prophylactic group seen between 1985 and 1990) were compared to controls with the same high risk voiding parameters who did not receive early therapy (observation group seen between 1978 and 1984 with therapy instituted 1 year or longer after high risk was noted). Of the 45 patients at risk, clean intermittent catheterization and anticholinergic medication were immediately initiated in 18, while 27 were treated expectantly. Patients in the observation group were followed an average of 4.1 years (range 1.1 to 14) before clean intermittent catheterization and anticholinergic medication were started. Of the 27 children treated expectantly 11 (41%) required augmentation, whereas only 3 of the 18 (17%) treated prophylactically required enterocystoplasty. When the number of augmentations was indexed to total years of follow-up in each of the 2 groups (296 versus 156 years) patients in the expectant group were nearly twice as likely to require augmentation. Identification and early proactive treatment of the high pressure, dyssynergic lower urinary tract significantly decreased the need for bladder augmentation as children with neurogenic bladder secondary to myelomeningocele mature.

CIC is not without its risks. Patients, who catheterize infrequently, may still generate high bladder pressures and be at risk for renal failure. Various authors report a variable incidence of catheter related infections but it is generally agreed that the risk is low as long as complete bladder emptying is achieved. It has also been proven that reuse of properly stored catheters don't lead to urinary tract infections. Symptomatic infections are mainly caused by incomplete bladder emptying, and CIC appliance by child or caregiver needs to be optimized. The frequency of CICs is also of paramount importance. Adolescents tend to socially more active and lead a busier life. It is important to train them to adhere to their self emptying schedules. This in itself is a daunting task for the parents and the role of treating physician and psychologist is very important. Surveillance of the CIC regimen during puberty is recommended because of adolescents seem to be rebellious and pose compliance issues. It is important to educate the adolescent about the consequences of UTI and kidney deterioration if CIC is either irregular or abandoned.

In a few children, a chronic subclinincal bacteruria may set in. These bacteria are generally of low clinical consequence to urinary tract health if they are evacuated on a regular basis of at least four or more times per day. Children with chronically colonized bladders will occasionally experience a symptomatic UTI requiring a course of antibiotic therapy. However, use of antibiotics should be reserved only for those infections associated with symptoms such as fever, urinary urgency, hematuria, or worsening incontinence. Pus cells are an unreliable predictor for symptomatic urinary infections. Cloudy or foul-smelling urine is a common phenomenon of the chronically colonized bladder, but does not necessitate antibiotic treatment. During such episodes, patients

should be encouraged to increase daily fluid intake, but avoid antibiotics that might disrupt the colonization of the bladder. 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. These are not suitable organisms to colonize the bladder and should be eradicated to minimize formation of urinary tract stones or biofilms. In general, other bacteria, such as E. coli and Klebsiella sp., can safely colonize the bladder.

There is a small group of patients in whom clean intermittent catheterization is not possible. Patients with cerebral palsy, paraplegia, limitations in arm function, body habitus, prior spinal fusion, or bracing may find CIC a difficult task. No uniform management can be recommended because these patients will usually have many other problems, including total dependence for daily care and unfitness for surgery. A permanent indwelling catheter may be the only option, and for those who are operable, a Mitrofanoff or Monti ileovesicostomy in the epigastrium may be advisable. There is little point in establishing a system that relies on catheterization by a caregiver every 4 hours because it is unlikely that there will be facilities for its continuation into adult life. It is almost impossible for a paraplegic woman to perform clean intermittent catheterization and a suprapubic catheterization site is needed.

But overall CIC has revolutionised the management of neurogenic bladders. Together with anticholinergic therapy, medical management has grown in stature and has been able to reduce the requirement of surgery in majority of patients. It is however essential to initiate early and ascertain complete and frequent emptying of the bladders. An adolescent on CIC can never have QOL scores similar to normal counterparts, however amongst the neurogenic bladder group, patients doing CICs successfully report a far better quality of life than those who are not well optimized.

Impact of Anticholinergics on the Quality of Life

Anticholinergic medications have a very important place in the management of patients with neuropathic bladders. Clean intermittent catheterization (CIC) in combination with anticholinergics (Fig. 2) is the most commonly employed therapy for children with neurogenic bladder dysfunction.[16] Oxybutynin hydrochloride is most commonly used anticholinergic agent, and long-term experience supports its safety also in newborns and infants. Neonates do not have a higher incidence of side effects than older children and anticholinergics can be started in infants safely.[8] Oxybutynin is a tertiary amine with a combination of anticholinergic, antispasmodic, local anesthetic and calcium-channel-blocking activity. Several studies have shown oxybutynin decreases the end filling pressure and leak point pressure, increases the maximal cystometric capacity of the neurogenic bladder, reduces the uninhibited detrusor contractions and preserves renal function. If the leak point pressure is below 40 cm H2O upper tract deterioration is unlikely. Detrusor overactivity in myelodysplasia is mainly neuropathic rather than secondary to functional outlet obstruction. The concept of a 'safe' bladder in myelomeningocele patients refers to avoiding more than 10 cm H2O increase in the vesical pressure at expected bladder capacity for age during filling phase. A leak point pressure exceeding 40 cm H2O may be beneficial for dryness but potentially harmful for the upper urinary tract.[17]

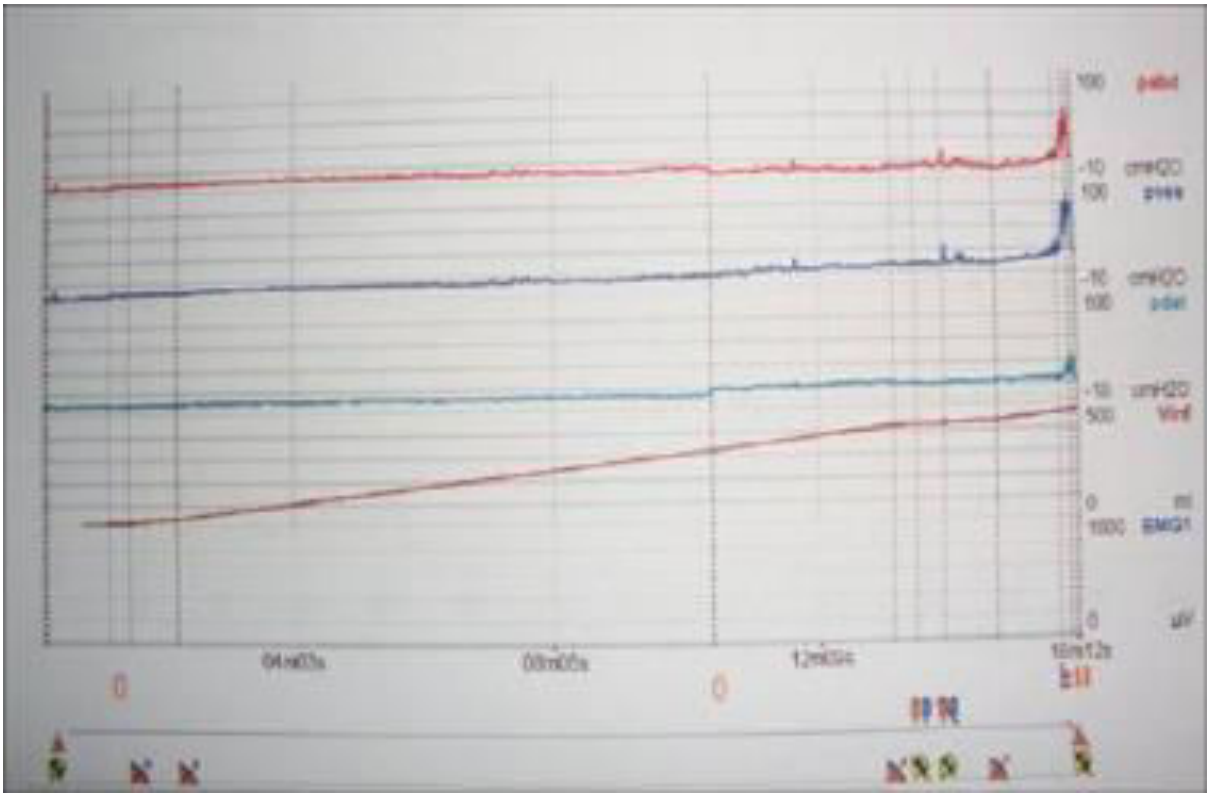

Fig. 2. Urodynamics of an adolescent with neurogenic bladder treated optimally with clean intermittent catheterization and anticholinergic medications; revealing a good capacity bladder with normal leak point pressure. (Age=13 years; Expected capacity=450ml; Maximal cystometric capacity=472ml; leak point pressure=26cmH2O)

However oxybutynin therapy has its own pitfalls. It has wide range of anticholinergic side effects like dry mouth, constipation, blurring of vision, headaches, dizziness, heat intolerance, personality changes and learning difficulties. About 10% patients drop out of treatment due side effects of oxybutynin. In addition twice or thrice a day dosing schedules don't help the compliance of the patients. Cost may be a limiting factor for many families. Oxybutynin can cause urinary retention in self voiders and therapy works well with CICs. Few bladders are refractory to oxybutynin therapy while others may become resistant to treatment over a period of time. Repeated or chronic infections have found to result in bladders refractory to anticholinergics. An elevated level of serum and urine Nerve Growth Factors were found in these patients.[18] Hence patients on anticholinergic therapy need to be monitored periodically. Compliance needs to be ensured and any worsening in the urodynamic parameters should be thoroughly investigated.

Recently, Buyse *et al* suggested that N-desethyl-oxybutynin, an active metabolite of oxybutynin, may be responsible for many anticholinergic side effects.[19] The levels of N-desethyl-oxybutynin relative to the parent compound are significantly lower when the drug is delivered intravesically. In children with insufficient response or significant systemic side effects to oral oxybutynin, intravesical instillation of oxybutynin has been shown to be a highly efficacious, reliable, and well-tolerated therapy for children who would otherwise require surgical therapy. Crushed oxybutynin tablets were used in the earlier trials, with consequent problems of inconvenience and impracticability and it led to poor patient compliance. With availability of specific formulations for intravesical use and elimination of the need for crushing tablets, intravesical oxybutynin therapy has become easy to use and acceptable for long-term therapy. 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. In addition, these pharmacokinetic studies provided evidence for a direct local rather than a systemic effect of intravesical oxybutynin on detrusor muscle. Further evidence for a local effect of intravesically administered oxybutynin was provided by studies showing local (urothelial) accumulation, suppression of muscarinic receptor- mediated detrusor muscle contractions, and blocking of muscarinic

receptors in bladder-afferent pathways. Intravesical oxybutynin can be given in as high doses as 0.9 mg/kg/day. However in children, intravesical administration has been reported to still cause significant anticholinergic side-effects, resulting in about a quarter of such patients stopping therapy.

Other bladder relaxant drugs include propiverine, trospium, darifenacin, solifenacin, fesoterodine and tolterodine. The current experience with compounds other than oxybutynin is still limited in children with neurogenic bladder. Propiverine, solifenacin and recently tolteridine are the most evaluated drugs for use in patients not responding to or not tolerating oxybutynin. A meta-nanlysis on these drugs found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride but not for oxybutynin orally administered, when currently used starting dosages were compared.[20]

As a potent and selective muscarinic receptor antagonist, solifenacin acts specifically at the M3 receptor site. Initial data have shown solifenacin to be more bladder-selective than its predecessors. It is this selective mode of action that gives solifenacin the potential to limit commonly experienced anticholinergic side effects. These developments could translate into higher patient compliance with the potential for better long-term results. Solifenacin has been shown to have a favorable risk/benefit ratio. At a once-daily oral dose of 5 mg/day, clinical data have shown solifenacin to be effective in reducing the symptoms of overactive bladder, with an incidence of dry mouth comparable to that associated with placebo. Results from phase I, II and III clinical trials have shown solifenacin to have a promising efficacy and safety profile for the treatment of overactive bladder. Comparative clinical trials are now needed to determine whether these initial results can prove solifenacin to be more beneficial than other commonly administered antimuscarinics.[21]

Tolterodine has been proven as effective as oxybutynin in treating detrusor overactivity in children but with fewer adverse events. Tolterodine is tolerated well in children even in subgroup of patients who could not tolerate oxybutynin chloride, 77% continued treatment with no significant side effects.[22] Goessl *et al*[23] in a comparative study between oxybutynin and tolterodine in children with myelomeningocele reported on 22 children, 10 of whom were crossed-over from oxybutynin to tolterodine because the side-effects were intolerable. The urodynamic effects were equivalent for both agents and only one patient had side-effects on tolterodine. Kilic *et al*[24] further found that the incidence of side-effects was low, with statistical significance in the tolterodine group (13 events in 13 patients) compared to oxybutynin group (27 events in 20 patients). In the oxybutynin group, eight patients were crossed over to tolterodine because of the severe side-effects of the oxybutynin. In a cross over study of 25 patients with neural tube defects, Extended release (ER) tolterodine once daily is as effective and well tolerated in children with neurogenic bladder as Immediate release tolterodine twice a day. ER formulation of tolterodine is less expensive and has the advantage of single dosage.

Among the other newer anticholinergics, data on the safety and efficacy in children is lacking. But propiverine hydrochloride was found to be effective in neurogenic detrusor overactivity in children and adolescents, even in some of those cases unresponsive to other anticholinergics. Bolduc *et al* also tried combination of more than one anticholinergic agents in refractory patients and found satisfactory results.[25] An alpha blocker or imipramine in combination with an anticholinergic has also been shown to be effective for certain refractory cases.

Botulinum A toxin injections into the detrusor muscle have been used in the treatment of neurogenic overactive bladder. Repeated botulinum A toxin injections could be considered to postpone or avoid surgical procedures in the children not responding to or not tolerating standard therapy with CIC and anticholinergics. However, further investigations are required, given remaining concerns about costs and long-term efficacy and safety of prolonged botulinum A toxin injections.

In recent years, it has become increasingly clear that treatment-related improvements in objective outcomes may not reflect subjective improvements in symptoms or other aspects of the condition that matter most to the patient. For example, patients may perceive a greater benefit from fewer incontinence episodes or a reduction in the amount of leakage, regardless of the number of episodes. It is likely that the impact of urinary symptoms will vary according to each patient's priorities and lifestyle. For example, urgency may have greater impact on a young professional who travels than it does on a person who is retired from the workforce. A patient's perception of treatment success should be regarded as an important measure of efficacy because patient considers the trade offs between symptom improvement, adverse effects and effects on daily life when assessing overall treatment benefit.

Impact of Augmentation Cystoplasty on the Quality of Life

Surgery is indicated in a number of patients who are not responding to the medical management. The surgeries vary according to the individual bladder dynamics and sphincter competence. Wherever the cause of neurogenic bladder can be treated surgically, it should be done on priority. Even if it does not cure the treatment it may be essential to avoid further deterioration in the neurologic status of the growing child.[26]

Patients with decreased urethral resistance and subsequent refractory incontinence pose a great surgical challenge, since there is no surgical procedure that has been proven to be uniformly successful. Pelvic floor strengthening is a feasible alternative for these patients and has shown to result in significant improvement in dry periods. However the results are not as good as in some other conditions because these patients may have dennervated pelvic floors rendered unfit for exercises. Attempts at bladder neck reconstruction include such procedures as the Kropp procedure, the Pippi Salle procedure, bladder neck suspensions, and slings and artificial urinary sphincters (AUS). Each procedure has advantages and disadvantages that need to be carefully explored with the patient and family. Whether the bladder volume acceptable and the urinary sphincter competent, or does the child require augmentation and/or an outlet resistance procedure to achieve continence is to be assessed carefully.

Broadly speaking the indications for enterocystoplasty can be absolute in the setting of upper tract deterioration due to high bladder storage pressure that is refractory to medical therapy. More commonly the indications are relative in the setting of socially unacceptable incontinence due to small capacity, detrusor overactivity and/or decreased compliance. The most objective indication for bladder augmentation is a documented bladder pressure of greater than 40 cm H2O. Increased bladder pressure can be seen intermittently due to detrusor overactivity or pressure may increase steadily during filling due to decreased compliance.

Many patients with neurogenic bladder may find it difficult to catheterize the native urethra (mentioned previously). These are candidates for catheterisable stomas. All continent catheterizable stomas employ a flap valve (Mitrofanoff) principal to maintain continence. Continence is achieved as the bladder fills and the intravesical pressure is transmitted to the conduit. If appendix is not available, ileum and colon can also be fashioned into a conduit utilizing the Monti procedure. In children who have failed conservative management of their fecal incontinence, the same Mitrofanoff and Monti principals can be applied to the creation of an antegrade continence enema (ACE).

The most commonly used segment for augmentation is ileum. Classic clamshell augmentation cystoplasty has been utilized successfully both in adults and in children. It is important to isolate the segment at least 10 cm from the ileocecal valve, so as not to interfere with bowel control, especially in patients with myelodysplasia who already have bowel continence issues. Sigmoid augmentation has also been successful, although there are reports of increased rhythmic contractions when this segment is used. In select cases, gastric augmentation has been quite successful. Proper patient selection, which includes neurogenic patients who are insensate, is critical to avoid the clinical syndrome of hematuria/dysuria. Gastric augmentation has the advantage of less mucous production and less changes in metabolic parameters. It would appear that there is little to choose between the various bowel segments used for reconstruction except that gastrocystoplasty seems to work better in this group than in others. The incidence of the hematuria/dysuria syndrome is only 10%-50% in various studies but it seems to be more diet related and altering dietary intakes is a very effective way to tackle hematuria dysuria syndrome. Gastrocystoplasty has significant advantages over intestinal augmentation, including decreased chloride reabsorption, mucous production and urinary infection, and an extremely low incidence of stones and perforation. The gastric patch is associated with metabolic alkalosis and the hematuria-dysuria syndrome (HDS), which may be avoided and medically treated with proper patient selection and close follow-up.

Rubenwolf *et al*[27] studied 44 children with irreversible lower urinary tract dysfunction who had a continent urinary diversion or enterocystoplasty over 15 years. The median (range) follow-up was 7.3 (3.5-17) years. Complete continence was achieved in 94% overall, *i.e.* in 95% of patients with continent cutaneous diversion and 83% with augmentation cystoplasty. Upper urinary tract and renal function remained stable in 89% and 95%, respectively. Surgical intervention was required for adhesive small bowel ileus in 6%, stoma-related complications in 39%, ureteric stenosis in 8%, and stone formation in 19%. Of these complications, 54% required only minor interventions, 41% of patients needed prophylactic alkaline substitution. Bowel habits remained unchanged or improved in 68%.

Herschorn *et al* reported a high degree of patient satisfaction following augmentation cystoplasty.[28] Fifty-nine patients, who had undergone augmentation enterocystoplasty as part of reconstruction mainly to correct hyperactive bladders and incontinence, were subjected to a questionnaire after a median of 76.1 postoperative months. The patients experienced a significant increase in bladder capacity and decrease in pressure at capacity ($P < 0.0001$). Normal upper tracts remained normal and there was either improvement or stabilization of

hydronephrosis. Twenty-four patients (40.6%) had one or more complications, with 21 requiring reinterventions. Twenty-five percent of patients required the reintervention within the first 25 months, and the median time to reintervention was almost 10 years. Thirty-five patients took medications such as anticholinergics, antidiarrheals, or antibiotics. Fifty-six patients were treated with clean intermittent catheterization (CIC) at a mean interval of 4.6 hours. Seven patients had some difficulty with CIC. Thirty-nine patients (67%) were dry, and 17 had mild and 3 severe incontinence. Eleven patients (18.6%) reported bowel dysfunction, although 7 had it preoperatively. Almost all patients were very satisfied with their urologic management.

There have been more than 20 reports of malignancy arising in the augmented bladders and although the risk appears minimal, it is showing a rising trend. Therefore surveillance of these augmented bladders is essential.

Augmentation is especially useful for transplant candidates for stabilization of bladder dynamics. Pediatric renal transplantation into a dysfunctional lower urinary tract yields outcomes comparable to transplantation into the normal lower urinary tract. Because of the high urologic complication rates, careful surveillance of lower urinary tract function by urodynamic evaluation is essential to optimize these outcomes.

Impact on the Caregivers and Society

The caregivers of children with spina bifida receive little attention. Raising a child with spina bifida is often a full-time occupation. For a working couple the stress may be tremendous. There is considerable emotional impact on the marital life of the parents and on the other children in the family. The financial implications are also considerable on the family and it assumes paramount importance in developing nations with lower per capita incomes. Financial instability may be a very important cause for non-compliance on the part of the care-givers.

In developing countries where most patients or parents can't afford a caretaker, one can take advantage of the still prevailing joint family traditions and grandparents can be motivated to be involved in full time care of these patients till they become self-dependent. For an unfortunate group of children, this may be life long.

In a study[29] on 39 adolescents with meningomyelocele, three-fourths of the parents rated their adolescent as happy and outgoing. Less than 10% noted a predominant angry or depressed mood. The majority of adolescents had three or more close friends. About 10% stated that their child had problems with alcohol or drugs. Parents evaluated the support they had received on the medical and physical aspect of their child's illness as greater than that on psychosocial issues (*e.g.*, sexuality, vocational needs). The desire for more assistance was expressed in these psychosocial areas (45% for sexuality and 68% for vocational needs) and in teenage issues (57%).

Role of Bowel Management in the Long Term Treatment of Neurogenic Bladder

Bladder management cannot be considered in isolation from bowel management. Constipation can cause incomplete bladder emptying even in healthy children. Bowel management programs should be initiated as early as possible. Many authors find it difficult to start after puberty. Neurogenic bowel dysfunction with constipation and fecal soiling can interfere with the institution of a successful CIC treatment. Retained stools may mechanically impair bladder filling, increase detrusor irritability, or contribute to urine retention. Stool incontinence increases the risk of bladder contamination and urinary tract infection.[6] For the sake of privacy, or when sitting on the toilet is a problem, an antegrade colonic enema stoma constructed from appendix may be used for bowel washouts. But the MACE procedure has not found popularity in the developing nations.

Sexual Function and Fertility in Patients of Neurogenic Bladder

In a study conducted by the department of psychiatry in Nederlands,[30] 17 adults with meningomyelocele were asked to participate in a study regarding their sexuality. 11 patients (8 males and 3 females) volunteered for the same. With 1 exception, all patients expressed a desire for sexual contact. Five of them masturbated and 6 patients sometimes had sexual contact. Eight patients had problems in the field of sexuality, but only 3 were dissatisfied with their present sexual life.

Sexuality is an important factor and patient satisfaction is largely dependent on his/her sexual fulfilment. It is of prime importance during puberty as this is the time when adolescents develop sexuality. Physically disabled children tend to experience delayed social and sexual growth. The severity of mental handicap in people with myelomeningocele, poor manual dexterity, lack of education, overprotective parents, and the problems that health professionals have addressing in the sexual issues of the physically disabled patients and their families

contribute to these delays. Such delays lead to the infantilization of this population and irreversible emotional trauma if they are not addressed early in childhood. Adequate psychosexual education of myelomeningocele patients and their families is a major social challenge. Incontinence, both fecal and urinary can significantly hamper an individual's confidence and make them apprehensive about their sexual performance. Proper counselling is essential and should include sex education, potential sexual and fertility problems, and treatment options for satisfactory function. Most studies concerning sexuality in this population revolve around erectile function in males, with sexual dysfunction in females rarely being discussed.

Erectile function is partly related to the level of the neurologic lesion. In a study[31] on 12 male patients with meningomyelocele, 10 were sexually active, with erection and ejaculation present in 9. Six male patients were having sexual intercourse and 1 had become a father. Most men experience erection but suffer from premature ejaculation. Such males can be treated with phosphodiesterase type 5 inhibitors or intracorporal injections but the results are variable. Males with sacral lesions have the best fertility potential; those suffering from lumbar lesions have loss of sensation over their phallus. A neurosurgical anastomosis between the ilioinguinal nerve and the dorsal penile nerve can restore some function. Higher lesions frequently have azoospermia.

Neurogenic Bladder in Adolescent Females

Females with neurogenic bladder are at a higher risk for renal failure compared to males. It is comparatively difficult for a female patient to initiate CIC on her own. Breast development at puberty makes it even more difficult. A wheel chair bound female may find it impossible to do CIC. Repeated radiation exposure remains a threat and especially in adolescent females pregnancy should be ruled out before undertaking any X-ray. Hyperreflexia associated with sexual intercourse worsens the bladder pressures. The presence of renal scars increases the risk of hypertension and can signal females who may be at risk of pre-eclampsia and hypertension during pregnancy.

In females, hormonal function is not impaired and fertility is considered to be normal, although menarche often spontaneously occurs at an earlier age than expected. In a study[31] on adult female patients with meningomyeloce, of the 35 female patients 24 were sexually active and 12 of the 17 having actual sexual intercourse had become pregnant. Of the latter 12 patients 10 had ileal conduit urinary diversions, and neither they nor their children experienced any major complications from pregnancy and delivery. To negate the increased risk of neuraltube defects in the children of patients with myelomeningocele folic acid therapy (4 mg/day) is recommended in all menstruating females. Urinary problems are commonly aggravated during pregnancy and delivery by Caesarian section is routinely advised.

Overall Impact on the Quality of Life

The quality of life in adolescents with neurogenic bladder greatly varies. But patients who have been optimized in the childhood and are now dry, usually have a satisfactory adulthood. In a Swedish study,[32] 26 adolescents with myelomeningocele were followed from birth. 18 had severe physical handicaps, and although there were equal numbers of males and females, more females have severe handicaps, 22 of the 26 had been educated in normal schools (19 in normal classes), but learning difficulties were common. Three other adolescent were mildly mentally retarded and one was severely so. Only seven had complete urinary continence. 19 took part in leisure-time activities, but many felt they had poor social contact with their schoolmates and one in three was competent in activities of daily living. In general, self-concept was poor and many had inadequate knowledge about sexuality and the cause of their handicap.

The worst group of patients is that have not been stabilized or optimized in childhood. These adolescents do badly. Progressive collapse of the spine with kyphoscolisis reduces the lung capacity. As the costal margin gets closer to the pubis, the abdominal cavity becomes less accessible for reconstructive surgery.[6] The greatest tragedy is the spina bifida patient who is incontinent or has an unmanageable stoma and is unfit for surgery. This problem is seen in 10% of adolescents, usually because of inadequate pulmonary function. It has been rightly quoted by Woodhouse,[6] "Bladder management must be defined in childhood. Everything gets worse in adolescence."

Reference:

1. Bajpai M. National survey on hydrocephalus & spina bifida (IAPS members): need for consensus conference. *Indian J Pediatr,* 64(6 Suppl): 86-94, 1997.
2. Bauer SB. Neurogenic dysfunction of the lower urinary tract in children. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. *7th ed. Philadelphia: W. B. Saunders Co.;* 1998.
3. Bajpai M. Spina bifida and intraspinal lipomas. *ANZ J Surg,* 64: 177-179, 1994.
4. Bajpai M, Kataria R, Bhatnagar V *et al.* Management of hydrocephalus. *Indian J Pediatr,* 64 (6 Suppl): 48-56, 1997.
5. Shin M, Besser LM, Siffel C. *et al.* Congenital anomaly multistate prevalence and survival collaborative prevalence of spina bifida among children and adolescents in 10 regions in the United States. *Pediatrics,* 126: 274-279, 2010.
6. Woodhouse CRJ. The fate of the abnormal bladder in adolescence. *J Urol,* 166: 2396-2400, 2001.
7. Puri A, Bajpai M. Non-surgical options in the treatment of urinary incontinence due to neurogenic bladder: pharmacotherapy, biofeedback, neuromodulation and clean intermittent catheterization. In: Bajpai M, Gearhart JP, editors. Progress in Pediatric Urology. 5th ed. London, New Delhi, Washington. *Penwel Publishers*, 2002.
8. Kaefer M, Pabby A, Kelly M, *et al.* Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. *J Urol,* 162: 1068-1071, 1999.
9. Kataria R, Bajpai M, Lall A *et al.* Neurogenic bladder: urodynamic and surgical aspects. *Indian J Pediatr,* 64 (6 Suppl): 68-76, 1997.
10. Kaplan WE, McLone DG, Richards I. The urological manifestations of the tethered spinal cord. *J Urol,* 140: 1285-1288, 1988.
11. Rickwood AMK, Mundy AR, Stephenson TP, *et al.* Neuropathic bladder in childhood. In: Mundy AR, Stephenson TP, Wein AJ, editors. Urodynamics: Principles, Practice and Application, 2nd ed. Edinburgh: *Churchil Livingstone;* 403-422, 1994.
12. DeLair SM, Eandi J, White MJ, *et al.* Renal cortical deterioration in children with spinal dysraphism: Analysis of risk factors. *J Spinal Cord Med,* 30: S30-34, 2007.
13. de Kort LMO, Bower WF, Swithinbank LV *et al.* The management of adolescents with neurogenic urinary tract and bowel dysfunction. *Neurourol Urodynam,* 31: 1-5, 2012.
14. Lawrenson R, Wyndaele JJ, Vlachonikolis I, *et al.* Renal failure in patients with neurogenic lower urinary tract dysfunction. *Neuro-epidemiology,* 20: 138-143, 2001.
15. Diokno AC, Sonda LP, Hollander JP, *et al.* Fate of patients started on clean intermittent self-catheterization therapy 10 years ago. *J Urol,* 129: 1120-1122, 1983.
16. Bajpai M, Kataria R, Gupta DK, Agarwala S. Occult spinal dysraphism. *Indian J Pediatr,* 64(6 Suppl): 62-67, 1997.
17. Neve´us T, von Gontard A, Hoebeke P, *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: Report from the Standardisation Committee of the International Children's Continence Society. *J Urol,* 176: 3144-3324, 2006.
18. Liu HT, Lin H, Kuo HC. Increased serum nerve growth factor levels in patients with overactive bladder syndrome refractory to antimuscarinic therapy. *Neurourol Urodyn,* 30: 1525-1529, 2011.
19. Buyse G, Waldeck K, Verpoorten C, *et al.* Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. *J. Urol,* 160: 892-896, 1998.
20. Kessler TM, Bachmann LM, Minder C, *et al.* Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. *PLoS One,* 6: e16718, 2011.
21. Chilman-Blair K, Bosch JL. Solifenacin: treatment of overactive bladder. *Drugs Today (Barc),* 40: 343-353, 2004.
22. Nijman RJ, Borgstein NG, Ellsworth P, Djurhuus JC. Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol,* 173: 1334-1339, 2005.
23. Goessl C, Sauter T, Michael T, *et al.* Efficacy and tolerability of tolterodine in children with detrusor hyperreflexia. *Urology,* 55: 414-418, 2000.

24. Kilic N, Balkan E, Akgoz S, Sen N, Dogruyol H: Comparison of the effectiveness and side-effects of tolterodine and oxybutynin in children with detrusor instability. *Int J Urol,* 13: 105-108, 2006.

25. Bolduc S, Moore K, Lebel S, *et al.* Double anticholinergic therapy for refractory overactive bladder. *J Urol,* 182: 2033-2038, 2009.

26. Bajpai M, Bhatnagar V, Mitra DK *et al.* Spina bifida occulta: radiographic and operative correlation. *Indian J Pediatr,* 56: 513-517, 1989.

27. Rubenwolf PC, Beissert A, Gerharz EW, Riedmiller H. 15 years of continent urinary diversion and enterocystoplasty in children and adolescents: the Würzburg experience. *BJU Int,* 105: 698-705, 2010.

28. Herschorn S, Hewitt RJ. Patient perspective of long-term outcome of augmentation cystoplasty for neurogenic bladder. *Urology,* 52: 672-678, 1998.

29. Rinck C, Berg J, Hafeman C. The adolescent with myelomeningocele: a review of parent experiences and expectations. *Adolescence,* 24: 699-710, 1989.

30. Vroege JA, Zeijlemaker BY, Scheers MM. Sexual functioning of adult patients born with meningomyelocele. A pilot study. *Eur Urol.,* 34: 25-29, 1998.

31. Cass AS, Bloom BA, Luxenberg M. Sexual function in adults with myelomeningocele. *J Urol,* 136: 425-426, 1986.

32. Börjeson MC, Lagergren J. Life conditions of adolescents with myelomeningocele. *Dev Med Child Neurol,* 32: 698-706, 1990.