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Preventing Kidney Injury in Children with Neurogenic Bladder Dysfunction

Faezeh Javadi Larijani, Mastaneh Moghtaderi, Nilofar Hajizadeh, Farahnak Assadi[1]

Department of Pediatrics, Division of Nephrology, Children Medical Center, Tehran University of Medical Sciences, Tehran, Iran, [1]Department of Pediatrics, Division of Nephrology, Rush University Medical Center, Chicago, IL, USA

Correspondence to:
Prof. Farahnak Assadi,
Department of Pediatrics, Division of Nephrology, Rush Children's Hospital, Rush University Medical Center, Chicago, 18 Scarlet Oak, Dr Haverford, PA 19041, USA.
E-mail: fassadi@rush.edu

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Review Article

ABSTRACT

The most common cause of neurogenic bladder dysfunction (NBD) in newborn infants is myelomeningocele. The pathophysiology almost always involves the bladder detrusor sphincter dyssynergy (DSD), which if untreated can cause severe and irreversible damage to the upper and lower urinary tracts. Early diagnosis and adequate management of NBD is critical to prevent both renal damage and bladder dysfunction and to reduce chances for the future surgeries. Initial investigation of the affected newborn infant includes a renal and bladder ultrasound, measurement of urine residual, determination of serum creatinine level, and urodynamics study. Voiding cystogram is indicated when either hydronephrosis or DSD is present. The main goal of treatment is prevention of urinary tract deterioration and achievement of continuance at an appropriate age. Clean intermittent catheterization (CIC) in combination with anticholinergic (oxybutynin) and antibiotics are instituted in those with high filling and voiding pressures, DSD and/or high grade reflux immediately after the myelomeningocele is repaired. Botulium toxin-A injection into detrusor is a safe alternative in patients with insufficient response or significant side effects to anticholinergic (oral or intravesical instillation) therapy. Surgery is an effective alternative in patients with persistent detrusor hyperactivity and/or dyssynergic detrusor sphincter despites of the CIC and maximum dosage of anticholinergic therapy. Children with NBD require care from a multidisciplinary team approach consisting of pediatricians, neurosurgeon, urologist, nephrologists, orthopedic surgeon, and other allied medical specialists.

Keywords: Anticholinergic, botulinum toxin, chronic kidney failure, clean intermittent catheterization, neurogenic bladder dysfunction

INTRODUCTION

Neurogenic bladder dysfunction (NBD) can develop as a result of a lesion at any level in the nervous system. However, the commonest cause of NBD is myelomeningocele.[1-4] Other causes of NBD involving the spinal cord include, spina bifida occulta, lipomeningocele, sacral agenesis, and tethered spinal cord associated with imperforated anus, and cloacal malformations.[1-4]

The incidence of meyelomeningocele ranges from 0.3 to 4.5/1,000 births in the general population. If the myelomeningocele is present in one child in a family, the chance of having a sibling with the same condition is 2-5%. The prevalence of this condition appears to be higher in the offspring of mothers who had folic acid deficiency during pregnancy.[5] However, folic acid replacement during the pregnancy did not decrease the disease prevalence. Currently no genetic markers have been linked to the presence of myelomeningocele.

At birth, most newborns with spina bifida have a normal upper urinary tract. However, the majority will develop deterioration of renal function and bladder-wall changes without adequate management.[6-8] Early proactive management improves upper urinary tract function and reduces the need for surgery in patients with spina bifida.[9,10] Progressive renal damage is due to high detrusor pressures both throughout the filling and emptying (poor compliance bladder) as well as superimposed detrusor contractions against a closed sphincter or detrusor sphincter dyssynergia (DSD).[4-11] Many children with NBD experience recurrent urinary infections, which can increase the risk for renal impairment. NBD-related kidney scarring has long been considered as the cause of substantial long-term morbidity in the form of hypertension and chronic kidney disease.[6-8]

To prevent renal damage, NBD must be treated immediately after birth following closure of the back lesion.[9,10] Remarkable progress has been made in the medical treatment of children with the NBD over the past few decades.[1,2,6,11-13] These advances are primarily due to the discovery of newer medications, the better understanding of the pathophysiology of NBD, the increased application of urodynamics study during infancy, and the functional classification of NBD into low- and high-risk groups.[11,14-16]

The use of a multidisciplinary team approach especially, one that incorporates increased data sharing using the enhanced health information technology, such as electronic records and electronic data transmission have made it possible to both safely and effectively eliminate incontinence and protect the upper urinary tract, and improve the patient's outcome and quality of life. The team includes pediatricians and other specialists from urology, neurosurgeon, nephrology, orthopedics, and physical medicine and rehabilitation.[17]

This review focuses on diagnosis, pathophysiology, and treatment of NBD in the newborn with spina bifida that have evolved in recent years.

PATHOPHYSIOLOGY

During normal voiding, the sphincter relaxes as the detrusor muscle contracts to allow unobstructed urinary flow. Spinal cord injury can lead to dyssynergy so that the sphincter is closed when the detrusor contracts, creating high pressures within the bladder but low flow rates. An increased intravesical pressure, the leak-point pressure (the bladder pressure at which urethral leakage occurs), or detrusor external sphincter dyssynergia are now recognized as significant risk factors of subsequent upper and lower urinary tracts deterioration. When the detrusor filling pressure exceeds 40 cm H_2O ureteral drainage into bladder deteriorates, leading to hydronephrosis and vesicoureteral reflux (VUR), recurrent urinary tract infections due to bladder residue, and ultimately renal insufficiency.[4,11,14,15,18,19]

Based on urodynamic studies, four subtypes of the NBD have been identified for defining the underlying the pathophysiology and treatment plan in affected children as follows: [11,15,16,20]

- Sphincter overactivity causing functional obstruction combined with a detrusor inactivity or a bladder that does not generate a contraction (type A). The result is that the bladder will not empty fully (urine retention)
- Another possible diagnosis is DSD, in which increased sphincter activity occurs during detrusor contraction (type B). This finding is significant because DSD has been associated with an increased risk of upper urinary tract deterioration in over 60% of patients[4,8,11]
- Sphincter denervation with no resistance to urine flow combined with detrusor inactivity (stasis) (type C). In this type the bladder leaks due to both large bladder capacity (stasis) and incompetent sphincter
- Sphincter denervation combined with detrusor hyperactivity (type D). In this type the bladder leaks due to detrusor hyperreflexia with detrusor hypertrophy and loss of bladder compliance.

Diagnostic evaluation

Although diagnosis of NBD in neonates with meningocele is obvious, recognition becomes more difficult in those with spina bifida occulta because most of the children have no clinical manifestation of this disease other than the cutaneous lesion.[4,11] The lumbosacral cutaneous lesions often signify an underlying bony and/or spinal cord malformation. The symptoms of difficulty emptying the bladder, slow stream while staining to void, frequency, and urgency that are highly suggestive of a NBD in older children are often absent or cannot be articulated during infancy.

In the newborn period, these infants appear normal with no lower extremity abnormalities, except for the lumbosacral cutaneous lesions. With time, they may develop difficulty in toilet training or urinary infection. Lower extremity neurologic deficits including urinary and/or fecal incontinence develop as the child grows and become evident around the time of puberty when growth spurt causes increased traction on the spinal cord. Toilet-trained young children may start wetting again; complain of abdominal pain, dysuria or urinary incontinence.[11]

When evaluating a child with NBD, a detailed history regarding previous urinary infection, trauma, voiding diary, and bowel habits should be obtained. Physical examination should include a thorough neurologic evaluation including, perianal sensation, anal sphincter tone reflexes in the sacral level, and deep tendon reflexes in the lower extremities.

Initial investigation in newborns should include urinalysis with urine culture, catheterized measurement of urine residual after voiding, renal, and bladder ultrasound, determination of serum creatinine level, and urodynamic studies combined with urethral sphincter electromyography (EMG).[4,11,14] Voiding cystography is indicated when hydronephrosis is present or urodynamic studies suggest risk to the upper urinary tract from an increased detrusor pressure at capacity or bladder sphincter dyssynergy.[4,11,15]

Urodynamics study should be carried out as soon as possible after birth to identify the high groups and individualized treatment planning based on the type of dysfunction.[16,20] The urodynamic study if properly performed, even in the newborn, provides measurement of post-voiding residual urine volume, bladder capacity, compliance, bladder filling, and voiding pressures, and urine flow rate. The EMG reveals the relationship between detrusor contractions and the urinary sphincter and allows recognition of the different subtypes of NBD.[4] The normal end filling pressure (the change in bladder filling pressure between emptying and storage) should be less than 10 cm H_2O while the normal voiding pressure varies from 55 cm to 80 cm of H_2O in boys and from 40 cm to 65 cm in girls.[4,11] The findings are considered normal when there is an appropriate capacity, good compliant bladder, and an increase in sphincter activity during filling and complete silencing during emptying.

Detrusor overactivity is defined as any short-lived pressure rise of greater than 15 cm H_2O from baseline before capacity is reached.[4,16] Risk factors are elevated detrusor filling pressure, DSD or high voiding or leaking pressures above 40 cm H_20 at capacity.[21]

The most common abnormal findings in the newborn infant is the failure of the sphincter to relax during a detrusor contraction or DSD (type B) which is usually associated with VUR and recurrent urinary infections while extensive denervation of the sphincter without contractions of the detrusor muscle (type C) is the most common abnormality in older children.[11]

Urodynamic testing may produce artificial information because of mechanical factors (such as elevated leak pressure or inability to void due to the catheter-induced bladder-outlet obstruction) and fast bladder filling rates above the natural filling leading to detrusor hypertonicity.[22] To avoid this rate of infusion should be set at 10% of the expected bladder capacity for age.[4] The expected normal bladder capacity (EPC) in milliliters is calculated using the following formulae: EPC = age (in years) + 30 × 30.[4]

The newborns should be evaluated at 3, 6 and 12 months. A renal ultrasound, urinalysis, and urodynamics study are obtained at each visit when indicated. After 6 months of age, the imaging modality is magnetic resonance imaging of the spine.

Management

The primary goal of treatment is to identify the lower urinary tract abnormalities that contribute to NBD and to highlight strategies to preserve the upper urinary tract integrity and provide continence at an appropriate age.[9,10,13,23,24]

Most infants with spina bifida present with elevated detrusor filling pressure, high leak-point pressure, and dyssynergic sphincter, dangerous combinations, which can cause severe and irreversible renal and damage.[4,11] To prevent renal damage treatment should start immediately after birth by Clean Intermittent Catheterization (CIC) and pharmacological suppression of detrusor overactivity.[23,24] CIC in combination with anticholinergic (oxybutynin) and antibiotics are instituted in those with high filling and voiding pressures, DSD and/or high grade reflux, immediately after closure of the back lesion.[13,23]

In patients with a high filling pressure and continuous leaking (type A), the CIC alone is the first-choice treatment to empty the bladder effectively. CIC is performed, 4-5 times a day. Sterile technique to empty bladder is necessary to avoid bladder infection. Starting CIC in newborns has led to easier acceptance by parents and children and reduced upper tract deterioration. The parent assumes the responsibility for bladder emptying when the child is unable to perform catheterization.[13]

When the DSD with high voiding and emptying pressures (>40 cm H_2O) present (type B), anticholinergic medications, such as oxybutynin, tolterodine, propiverine or trospium in combination with CIC can successfully lower the filling and emptying pressures through suppression of detrusor overactivity and converting the NBD type B to type A, which has to be emptied with CIC.[6,24]

Oxybutynin hydrochloride is the most commonly used anticholinergic agent in newborns and infants.[7,22,25,26] The usual dose regimen of oral oxybutynin is 0.3-0.6 mg/kg per day in three divided doses. Intravesical instillation of oxybutynin has been shown to be a highly efficacious, reliable, and well-tolerated therapy for children who fail to response or have significant systemic adverse effects to oral oxybutynin therapy.[27-30]

Alpha-adrenergic blockers have been used to facilitate bladder emptying in patients with NBD. However, their use is considerably limited by their undesirable systemic side effects.[31] Likewise, tricyclic antidepressants, such as imipramine and amitriptyline hydrochloride, are not widely used due to their serious cardiovascular and systemic toxic effects.

Botulinum toxin-A is a safe alternative in the management of detrusor hyperreflexia in children with insufficient response or significant systemic side effects to anticholinergic therapy.[32-35] Endoscopic injections of botulinum toxin A (Botox) 10 U/kg (maximum 300 U) into the detrusor blocks release of acetylcholine at the neuromuscular junction causing transient smooth muscle paralysis and improving urinary incontinence.[33] Patients may be considered for reinjection when the clinical effect of the previous injection diminishes (median 6-12 months in most patients). Repeat injections of botulinum toxin A have been shown to be safe and do not lead to increased risk of fibrosis in the bladder wall.[35]

CIC and surgical procedures are used in children with an incompetent sphincter and acontractile bladder detrusor (type C) while CIC combined with anticholinergics and bladder-outlet surgery are used in those with incompetent sphincter and detrusor overactivity (type D).[36,37]

When medical treatment fails, surgical procedures need to be considered to achieve continence. Various bladder outlet surgeries including injection of bulking agents at the bladder neck, transurethral sphincterotomy, artificial sphincter implantation, urethral and bladder neck procedures have been used to increase resistance, but no one procedure is ideally suited for every patient.[38-41] Bowel augmentation onto the bladder are frequently used for bladder augmentation; however, post-surgical complications including mucus production, recurrent urinary infections, stone formation, and the risk for late occurrence of cancer in the augmented segment limit its application.[42]

Electrostimulation of the sacral nerve have been used in children for treatment of overactive bladder and urinary incontinence and may offer a valuable option to a definitive surgery.[43,44] The technique is safe and more effective than the conservative treatment for incontinence.[43,44] Engineered bladder tissue and a stem cell therapy for bladder enlargement are currently under evaluation, and the preliminary results have been promising.[45]

All the febrile urinary tract infections must be treated with antibiotics as soon as possible. Patients with recurrent symptomatic urinary infections who have reflux should be treated with prophylactic antibiotics. Asymptomatic bacteriuria is common but does not require treatment. NBD children also experience chronic constipation with bowel incontinence, which can be treated with mild laxatives, such as mineral oil, retrograde or antegrade or enemas.

CONCLUSIONS

Spina bifida is the most common cause of NBD in children. The pathophysiology almost always involves dyssynergia between the bladder detrusor musculature and external bladder sphincter, which if untreated can adversely affect bladder function and cause secondary damage of the upper urinary tract. Early diagnosis and adequate management during infancy can prevent both renal damage and bladder dysfunction and to achieve urinary continence at an appropriate age.

Initial baseline evaluation should include, renal and bladder ultrasonography, urinalysis with urine culture, and determination of serum creatinine level urodunamiic studies shortly after birth followed by voiding cystography if indicated.

Treatment strategies must focus on protecting the upper tract, maintaining a low-pressure reservoir, achieving complete bladder emptying and safe urinary continence. CIC combined with anticholinergics (oral or intravesical) is the first-line of therapy in newborns with NBD. Endoscopic injection of botulinum toxin is considered for patients who fail or cannot tolerate the adverse effects of anticholinergic therapy while surgical procedures with CIC are instituted in those when DSD, elevated leak point pressure, and/or reflux grade 3 or higher are present. Electrostimulation of the sacral nerve and artificial tissue engineering for bladder augmentation may offer a valuable option instead of a definitive surgery in the future.

REFERENCES

1. Mourtzinos A, Stoffel JT. Management goals for the spina bifida neurogenic bladder: A review from infancy to adulthood. Urol Clin North Am 2010;37:527-35.
2. Frimberger D, Cheng E, Kropp BP. The current management of the neurogenic bladder in children with spina bifida. Pediatr Clin North Am 2012;59:757-67.
3. Amarante MA, Shrensel JA, Tomei KL, Carmel PW, Gandhi CD. Management of urological dysfunction in pediatric patients with spinal dysraphism: Review of the literature. Neurosurg Focus 2012;33:E4.
4. Bauer SB. Neurogenic bladder: Etiology and assessment. Pediatr Nephrol 2008;23:541-51.
5. Rothenberg SP, da Costa MP, Sequeira JM, Cracco J, Roberts JL, Weedon J, *et al*. Autoantibodies against folate receptors in women with a pregnancy complicated by a neural-tube defect. N Engl J Med 2004;350:134-42.
6. Shin M, Kucik JE, Siffel C, Lu C, Shaw GM, Canfield MA, *et al*. Improved survival among children with spina bifida in the United States. J Pediatr 2012;161:1132-7.
7. Satar N, Bauer SB, Scott RM, Shefner J, Kelly M, Darbey M. Late effects of early surgery on lipoma and lipomeningocele in children less than 1 year old. J Urol 1997;157:1434-7.
8. Kari JA. Neuropathic bladder as a cause of chronic renal failure in children in developing countries. Pediatr Nephrol 2006;21:517-20.
9. Filler G, Gharib M, Casier S, Lödige P, Ehrich JH, Dave S. Prevention of chronic kidney disease in spina bifida. Int Urol Nephrol 2012;44:817-27.
10. Lehnert T, Weisser M, Till H, Rolle U. The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity. Int Urol Nephrol 2012;44:335-41.
11. Verpoorten C, Buyse GM. The neurogenic bladder: Medical treatment. Pediatr Nephrol 2008;23:717-25.
12. Himsl KK, Hurwitz RS. Pediatric urinary incontinence. Urol Clin North Am 1991;18:283-93.
13. Edelstein RA, Bauer SB, Kelly MD, Darbey MM, Peters CA, Atala A, *et al*. The long-term urological response of neonates with myelodysplasia treated proactively with intermittent catheterization and anticholinergic therapy. J Urol 1995;154:1500-4.
14. Lavallée LT, Leonard MP, Dubois C, Guerra LA. Urodynamic testing – Is it a useful tool in the management of children with cutaneous stigmata of occult spinal dysraphism? J Urol 2013;189:678-83.
15. Drzewiecki BA, Bauer SB. Urodynamic testing in children: Indications, technique, interpretation and significance. J Urol 2011;186:1190-7.
16. Bauer SB, Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, *et al*. Predictive value of urodynamic evaluation in newborns with myelodysplasia. JAMA 1984;252:650-2.
17. Sarica K, Erbağci A, Yağci F, Yurtseven C, Buyukbebeci O, Karakurum G. Multidisciplinary evaluation of occult spinal dysraphism in 47 children. Scand J Urol Nephrol 2003;37:329-34.
18. Bauer SB, Joseph DB. Management of the obstructed urinary tract associated with neurogenic bladder dysfunction. Urol Clin North Am 1990;17:395-406.

19. Bauer SB, Labib KB, Dieppa RA, Retik AB. Urodynamic evaluation of boy with myelodysplasia and incontinence. Urology 1977;10:354-62.
20. Perez LM, Khoury J, Webster GD. The value of urodynamic studies in infants less than 1 year old with congenital spinal dysraphism. J Urol 1992;148:584-7.
21. Seki N, Akazawa K, Senoh K, Kubo S, Tsunoda T, Kimoto Y, *et al*. An analysis of risk factors for upper urinary tract deterioration in patients with myelodysplasia. BJU Int 1999;84:679-82.
22. Joseph DB. The effect of medium-fill and slow-fill saline cystometry on detrusor pressure in infants and children with myelodysplasia. J Urol 1992;147:444-6.
23. Kessler TM, Lackner J, Kiss G, Rehder P, Madersbacher H. Early proactive management improves upper urinary tract function and reduces the need for surgery in patients with myelomeningocele. Neurourol Urodyn 2006;25:758-62.
24. Guys JM, Hery G, Haddad M, Borrionne C. Neurogenic bladder in children: Basic principles, new therapeutic trends. Scand J Surg 2011;100:256-63.
25. Madersbacher H. Neurogenic bladder dysfunction in patients with myelomeningocele. Curr Opin Urol 2002;12:469-72.
26. Baskin LS, Kogan BA, Benard F. Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. Br J Urol 1990;66:532-4.
27. Buyse G, Verpoorten C, Vereecken R, Casaer P. Intravesical application of a stable oxybutynin solution improves therapeutic compliance and acceptance in children with neurogenic bladder dysfunction. J Urol 1998;160:1084-7.
28. Amark P, Bussman G, Eksborg S. Follow-up of long-time treatment with intravesical oxybutynin for neurogenic bladder in children. Eur Urol 1998;34:148-53.
29. Haferkamp A, Staehler G, Gerner HJ, Dörsam J. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. Spinal Cord 2000;38:250-4.
30. Buyse G, Waldeck K, Verpoorten C, Björk H, Casaer P, Andersson KE. Intravesical oxybutynin for neurogenic bladder dysfunction: Less systemic side effects due to reduced first pass metabolism. J Urol 1998;160:892-6.
31. Husmann DA. Use of sympathetic alpha antagonists in the management of pediatric urologic disorders. Curr Opin Urol 2006;16:277-82.
32. Dyer LL, Franco I. Botulinum Toxin-A therapy in pediatric urology: Indications for the neurogenic and non-neurogenic neurogenic bladder. Scientific World Journal 2009;9:1300-5.
33. Pascali MP, Mosiello G, Boldrini R, Salsano ML, Castelli E, De Gennaro M. Effects of botulinum toxin type a in the bladder wall of children with neurogenic bladder dysfunction: A comparison of histological features before and after injections. J Urol 2011;185:2552-7.
34. Watanabe JH, Campbell JD, Ravelo A, Chancellor MB, Kowalski J, Sullivan SD. Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder. Urology 2010;76:835-40.
35. Riccabona M, Koen M, Schindler M, Goedele B, Pycha A, Lusuardi L, *et al*. Botulinum-A toxin injection into the detrusor: A safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. J Urol 2004;171:845-8.
36. Joseph DB. Current approaches to the urologic care of children with spina bifida. Curr Urol Rep 2008;9:151-7.
37. de Jong TP, Chrzan R, Klijn AJ, Dik P. Treatment of the neurogenic bladder in spina bifida. Pediatr Nephrol 2008;23:889-96.
38. Guys JM, Breaud J, Hery G, Camerlo A, Le Hors H, De Lagausie P. Endoscopic injection with polydimethylsiloxane for the treatment of pediatric urinary incontinence in the neurogenic bladder: Long-term results. J Urol 2006;175:1106-10.
39. Lottmann HB, Margaryan M, Bernuy M, Grosz A, Aigrain Y, Lortat-Jacob S, *et al*. Long-term effects of dextranomer endoscopic injections for treatment of urinary incontinence: An update of a prospective study of 31 patients. J Urol 2006;175:1485-9.
40. Snodgrass W, Barber T. Comparison of bladder outlet procedures without augmentation in children with neurogenic incontinence. J Urol 2010;184:1775-80.
41. Churchill BM, Bergman J, Kristo B, Gore JL. Improved continence in patients with neurogenic sphincteric incompetence with combination tubularized posterior urethroplasty and fascial wrap: The lengthening, narrowing and tightening procedure. J Urol 2010;184:1763-7.
42. Metcalfe PD, Rink RC. Bladder augmentation: Complications in the pediatric population. Curr Urol Rep 2007;8:152-6.
43. Lordêlo P, Teles A, Veiga ML, Correia LC, Barroso U Jr. Transcutaneous electrical nerve stimulation in children with overactive bladder: A randomized clinical trial. J Urol 2010;184:683-9.
44. Haddad M, Besson R, Aubert D, Ravasse P, Lemelle J, El Ghoneimi A, *et al*. Sacral neuromodulation in children with urinary and fecal incontinence: A multicenter, open label, randomized, crossover study. J Urol 2010;184:696-701.
45. Atala A. Tissue engineering of human bladder. Br Med Bull 2011;97:81-104.

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