REVIEWS IN UROLOGY

Recent Advances in Managing Pediatric Neurogenic Bladder due to Spina Bifida

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Abstract

Background: Spina bifida is the most prevalent permanently disabling birth defect in the world. It results in damage to nerve endings that negatively affect bladder function and can potentially lead to kidney failure. Management of spina bifida continues to evolve, however, improving outcomes for patients with this condition.

Methods: We performed a review of literature published in the past 10 years for advances in the prenatal and postnatal evaluation and treatment of pediatric patients with neurogenic bladder caused by spina bifida.

Results: Here, we discuss advances in prenatal surgical management and the implications for postnatal bladder function. Advances in urologic testing for patients with spina bifida, including urodynamics, imaging studies, and laboratory results, are presented, as are advances in surgical management of hostile neurogenic bladder.

Conclusion: The management of pediatric neurogenic bladder resulting from spina bifida continues to improve. Future advances based on tissue engineering and artificial intelligence remain to be evaluated.

Introduction

Bladder function relies on a complex interplay of nerves and muscles to allow for normal bladder filling and emptying. Neural tube defects, such as spina bifida, result in damage to nerve endings, which in turn negatively affects bladder function. Spina bifida is the most prevalent permanently disabling birth defect in the world; the primary goal of urologic care for this patient population is to preserve normal kidney function through safe bladder pressure maintenance. We present a review of recent advances in the prenatal and postnatal evaluation and treatment of pediatric patients with neurogenic bladder caused by spina bifida.

Prenatal Evaluation

Spina bifida is typically diagnosed during the second trimester of pregnancy via high-resolution ultrasound.[1] Ultrasound can detect the location and size of the spinal cord lesion, the presence of hydrocephalus, and usually whether the lesion is open or closed.[1] Fetal magnetic resonance imaging (MRI) is used as the second-line imaging modality to provide additional anatomical detail. One challenge of fetal MRI is uninhibited fetal motion; therefore, various superresolution techniques have been used to produce better MRI images.[2]

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Advances in MRI techniques provide better anatomical detail, and the diffusion MRI technique also shows promise for evaluating white matter development and upstream neural damage; in the future, it may even be able to predict neurodevelopmental outcomes.[2]

Prenatal Closure

The sequelae of spina bifida result from damage to the delicate exposed nerves. The Management of Myelomeningocele Study (MOMS) trial was conducted to determine whether fetal surgery for spina bifida would mitigate the long-term sequelae seen in patients undergoing postnatal closures.[3] The optimal timing of fetal surgery is under investigation. Patients in the MOMS trial underwent surgery between 19 and 25 weeks' gestation, a time frame extrapolated largely from animal studies.[3] Because some cases of spina bifida are not diagnosed until later in gestation, Etchegaray et al[4] compared maternal and fetal outcomes for patients undergoing prenatal closure before 26 weeks' gestation with patients undergoing prenatal closure between 26 weeks' and 27 weeks 6 days' gestation. The authors found similar maternal and perinatal outcomes for both groups, indicating that prenatal surgery can be performed at up to 27 weeks 6 days' gestation.[4]

Although the MOMS trial demonstrated better brainstem function, lower hydrocephalus occurrence, and better motor function in patients treated prenatally, data are mixed on the urologic benefits of prenatal closure.[3] Initial short-term urologic follow-up of MOMS trial patients showed no difference in the need for clean intermittent catheterization at 30 months.[5] In a single-institution study, Zaccaria et al[6] found that infants undergoing postnatal closure were more likely to be discharged on clean intermittent catheterization, but at a median follow-up of 36 months there was no difference in use of clean intermittent catheterization between prenatal and postnatal closure groups. Similarly, Zaccaria et al[6] found no notable difference in risk for postnatal anticholinergic use between prenatal and postnatal closure. Follow-up of children from the MOMS trial at school age demonstrated increased volitional voiding and decreased need for anticholinergics and clean intermittent catheterization in the prenatal closure group.[7] These results must be interpreted with caution, however, because there were no differences in urodynamics between the prenatal and postnatal closure groups; the subjective results were based purely on parental reports.[7] Macedo et al[8] conducted a prospective study of patients who underwent in utero repair and reported little benefit in bladder function, defined by high-risk bladder pattern, incontinence, and underactive bladder, compared with published data for postnatal repair. Parizi et al[9] performed a retrospective review of their myelomeningocele closure database, and they reported a lack of improvement in urologic parameters for in utero vs postnatal closure. They did find a higher prevalence of detrusor overactivity in the in utero closure group, but there was no statistically significant difference in any other urodynamics parameters.[9]

Most recently, open vs fetoscopic prenatal myelomeningocele closure has been investigated.[10] Gerber et al[10] performed a retrospective analysis of patients undergoing myelomeningocele closure at their institution and concluded that the incidence of high-risk bladder pattern on urodynamics was lower in fetoscopic prenatal closures than in prenatal open closures and traditional postnatal open repair. In addition, the incidence of hydronephrosis was lowest in the fetoscopic prenatal repair group.[10] Both procedures carry risks, such as elevated risk of preterm delivery, uterine dehiscence resulting from scarring complications, and the necessity for cesarean delivery for open repair; fetoscopic repair carries the additional risk of preterm premature rupture of membranes resulting from an inability to close insertion sites, therefore also potentially leading to preterm delivery.[11]

ABBREVIATIONS

HCP	health care professional
MOMS	Management of Myelomeningocele Study
MRI	magnetic resonance imaging
QOL	quality of life
UMPIRE	Urologic Management to Preserve Initial Renal Function
UTI	urinary tract infection

As prenatal care for patients with spina bifida continues to improve, the urologic benefits of prenatal closure remain to be seen. There are the clear benefits of reduced hydrocephalus and improved motor function, however, so as techniques for closure become more advanced and more common, we may be able to better study the long-term outcomes of prenatal closure on bladder function.

Postnatal Evaluation

The effects of spina bifida on bladder function are different for each patient. Therefore, thorough evaluation and close monitoring of kidney and bladder function are imperative to mitigate long-term kidney damage. To help standardize the initial urologic evaluation and treatment of patients with neurogenic bladder due to spina bifida, the Urologic Management to Preserve Initial Renal Function (UMPIRE) protocol was introduced in 2015.[12] Ultrasound, urodynamics, dimercaptosuccinic acid scan, and blood work are the urologic monitoring tools currently available, and we present the most recent advances for these tests.

RENAL BLADDER ULTRASOUND

Renal bladder ultrasound is the most frequently used tool for monitoring kidney and bladder function in patients with spina bifida. Ultrasound is a noninvasive method that evaluates kidney function through the presence of hydronephrosis, increased echogenicity, renal scarring, ureteral dilation, or bladder wall thickening, the presence of any of which can prompt further testing.[13,14]

URODYNAMICS

Urodynamics is currently the best tool available to assess bladder function. Many protocols recommend proactive scheduling of urodynamics during child development to facilitate early identification and intervention for hostile bladders because imaging of the urinary tract can appear normal in the early stages of a hostile bladder.[13,15]

Defining a hostile bladder on urodynamics, and interpreting urodynamics in general, has been shown to have interrater and intrarater variability. The UMPIRE protocol aimed to standardize the definition of *hostile bladder* as end filling pressure or detrusor leak point pressure greater than or equal to 40 cm H_2O.[16] More recent studies, however, suggest that hostile bladder should be defined at a lower detrusor leak point pressure or end filling pressure.[17] To improve the interpretation of urodynamics and limit reader variability, research on new urodynamic parameters is under way. Tiryaki et al[18] evaluated the ratio of area under the cystometry curve to a detrusor leak point pressure–adjusted total area and calculated pressure measures (upper mean static pressure and theoretical end filling pressure) through retrospective chart review. They concluded that these measurements are more reliable than other urodynamic measures in predicting hydronephrosis and new scar formation.[18] Wang et al[19] used machine learning to create a mathematical model that accurately identified 81.35% of detrusor overactivity events across 799 urodynamic studies. Hobbs et al[20] also developed a machine learning algorithm to objectively identify detrusor overactivity during urodynamics solely among patients with spina bifida and accurately identified detrusor overactivity 91.9% of the time. It is possible that these techniques could eliminate the interrater variability of interpreting urodynamic studies.

Another limitation of urodynamics is patient and family compliance with frequent testing in the clinic, which requires time off work and transportation and can be stressful. To facilitate frequent bladder pressure monitoring, Cooper et al[21] developed the cystomanometer, a handheld device with wireless data transmission for in-home use. The cystomanometer is a device that is easily added to the catheter to measure opening bladder pressures, and the data are then transmitted to recipients via Bluetooth.[21] Modifications to the design will be made, but data from the devices are strongly correlated with data from simultaneous urodynamics.[21,22] Huen et al[23] also recommended home bladder pressure measurements with manometry using a ruler and catheterization equipment; they found a correlation with urodynamic storage pressures and high-grade hydronephrosis in children with spina bifida. Home bladder measurements have the

potential to help monitor high-risk patients and alert the patient and their care team to the need for early urodynamic testing as well as to tailor catheterization and medication regimens.[21,23]

Alternatives to urodynamics have also been investigated. Bortolini et al[24] suggested dynamic ultrasonography as a noninvasive alternative to urodynamics to identify detrusor overactivity for patients with spina bifida. Investigators simultaneously compared dynamic ultrasonography with urodynamics and reported that dynamic ultrasonography was 90% accurate in detecting detrusor overactivity.[24] Dynamic ultrasonography is limited, however, in that it cannot replace urodynamics for evaluation of dynamic detrusor pressure values or of static pressures of compliance.[24] Another proposed noninvasive alternative to urodynamics is ultrasound-estimated bladder weight. Hwang et al[25] identified a bladder to body weight index that would predict the presence of high-pressure bladder and thus have the potential to enable clinicians to screen for and decrease cumulative urodynamic studies among patients.

DIMERCAPTOSUCCINIC ACID RENAL SCAN

A baseline dimercaptosuccinic acid renal scan is also recommended in several protocols and guidelines to evaluate for baseline kidney function and scarring. Data show that more than 90% of infants will have a normal baseline dimercaptosuccinic acid renal scan.[13] Given that the dimercaptosuccinic acid renal scan involves a needle stick, is lengthy, and exposes the patient to radiation, it is probably useful only for the subset of patients with febrile urinary tract infections (UTIs) or with renal scarring or echogenic kidneys on kidney ultrasound.[26]

LAB WORK

Historically, serum creatinine has been the standard laboratory test to measure kidney function (glomerular filtration rate), but patients with spina bifida often have low muscle mass, making this marker less accurate. Serum cystatin C can also be used to calculate glomerular filtration rate and may have greater sensitivity for detecting chronic kidney disease progression. Alternatively, Nayak et al[27] proposed urinary tissue inhibitor of metalloproteinase-2 as a noninvasive initial diagnostic marker for and predictor of neurogenic bladder in patients with spina bifida. The authors found that levels of tissue inhibitor of metalloproteinase-2 correlated with unsafe bladders on urodynamics, and there was also a statistically significant difference between patients with neurogenic bladder on and not on treatment.[27] If this test becomes more widely available, it would be a convenient, noninvasive way to monitor neurogenic bladder.

Postnatal Treatment

Management of neurogenic bladder in patients with spina bifida can be categorized as proactive or reactive and expectant.[15] Current literature points toward the benefits of early diagnosis and proactive management (early catheterization and use of anticholinergics) in improving long-term outcomes for patients with UTIs and in preventing kidney dysfunction and surgical procedures.[28,29] Not all families are willing or able to comply with these regimens, however, and for some patients the risks of these interventions may outweigh the benefits.

MEDICATIONS

Anticholinergics

Anticholinergics are used to decrease bladder contractility and thus decrease detrusor overactivity and improve bladder pressures. Historically, oxybutynin has been the first-line anticholinergic medication prescribed for neurogenic bladder.[30] Tolterodine, fesoterodine, and solifenacin are alternative anticholinergic medications that have been studied in children with neurogenic bladder; they have been found to be equally effective to oxybutynin.[31] Side effects, including dry mouth, constipation, gastroesophageal reflux, blurry vision, urinary retention, and altered cognition, remain the limiting factors in the use of anticholinergics.[31] Studies in older adults (ie, ≥65 years of age) have shown the negative effect of anticholinergics on cognition, but studies in the pediatric population have not shown the same negative effect, although more robust studies with longer follow-up are needed.

β3 Agonists

β3 Agonists are a newer class of medications for treating neurogenic bladder. They can be used alone or in combination with anticholinergics to optimize medical treatment for hostile neurogenic bladders. Mirabegron received US Food and Drug Administration approval for use in the pediatric population in 2021.[32,33] Vibegron is a newer β3 agonist has been demonstrated to be well tolerated, with urodynamic effectiveness in pediatric patients with anticholinergic-resistant neurogenic bladder dysfunction.[32,34,35] Aoki et al[34] reported statistically significantly greater bladder compliance and maximum cystometric bladder capacity with vibegron compared with anticholinergic agents in patients with spina bifida. Vibegron is currently in phase 2 clinical trials for Food and Drug Administration approval in the pediatric population. β3 Agonists have a more favorable side effect profile than anticholinergics, which makes them an attractive option for patients who cannot tolerate anticholinergics. The most common side effects include headache and hypertension, so blood pressure should be checked before the patient begins such medication and monitored at follow-up visits.[32,35]

CLEAN INTERMITTENT CATHETERIZATION

Medication alone typically is not adequate to treat neurogenic bladder; most patients also need clean intermittent catheterization for adequate bladder drainage. Debate is ongoing as to which catheters are superior and whether they should be single use or reused. Burki et al[36] reported that there was no statistically significant difference in complication rates for urethral clean intermittent catheterization when uncoated vs hydrophilic-coated catheters are used when looking at difficulty of insertion, recurrent UTIs, gross hematuria, or acute retention; however, the hydrophilic-coated catheters are 7 times costlier than standard catheters. In addition, Burki et al[36] reported that because of convenience of use, a clinically significant number of patients prefer the hydrophilic-coated catheters. As for single-use vs reused polyvinylchloride catheters, Madero-Morales et al[37] reported no difference in UTI or bacteriuria rates between the 2 catheters when a clean technique was used in patients with neurogenic bladder.

One concern with clean intermittent catheterization is the risk for recurrent UTIs. If patients do not empty their bladder by catheterization, however, they are also at elevated risk for recurrent infection. It can be challenging to diagnose a UTI in a patient on intermittent catheterization because they typically have bacteria present on urine culture, despite not being symptomatic. Therefore, it is important to consider the patient's symptoms in addition to culture results before starting antibiotics. If a patient is found to have recurrent UTIs while on intermittent catheterization, causes other than catheterization must be considered, such as worsening bladder dynamics, stones, constipation, and correct catheterization technique. It is important to note that antibiotic prophylaxis is not recommended in the setting of intermittent catheterization. The UMPIRE protocol calls for prophylaxis only in the setting of grade 5 vesicoureteral reflux or hostile bladder.[16]

BOTULINUM TOXIN A

Botulinum toxin A injection is a safe and effective treatment for improvement of bladder capacity, neurogenic detrusor overactivity, elevated bladder pressures, and refractory neurogenic bladder dysfunction in children.[38-40] A dose of 200 U per treatment shows the greatest reduction in bladder pressures and increase in bladder capacity.[41] There have been reports of poor responses, however, in patients with poorly compliant bladders without detrusor overactivity and decreased efficacy associated with long-term use.[42,43]

Botulinum toxin A bladder injections were initially performed via cystoscopy under general anesthesia. Recent practice patterns have shifted, however, and the procedure is now being offered as a well-tolerated office procedure without the need for anesthesia.[44] Electromotive drug administration is an alternative mode of botulinum toxin A delivery that does not require anesthesia and may lead to the same or better urodynamic improvements.[44,45] Ladi-Seyedian et al[45] compared intravesical botulinum toxin

A with electromotive drug administration and found that improved urodynamic parameters were better sustained at 1 year with electromotive drug administration. Of note, electromotive drug administration is still in the experimental phase, and additional research is necessary to determine the risks and benefits of treatment.

Botulinum toxin A bladder injection has the potential to extend the window for necessary bladder augmentation in patients with hostile neurogenic bladder.[46] A review of the Pediatric Health Information System database over the past decade, however, showed no difference in time at bladder augmentation for patients with spina bifida undergoing botulinum toxin A injections.[47]

SACRAL NEUROMODULATION

Sacral neuromodulation has been used in patients with nonneurogenic detrusor overactivity and underactivity for whom medical management fails. Because sacral neuromodulation relies on an intact nervous system, it was originally not offered as a treatment option for neurogenic lower urinary tract dysfunction. Chen et al[48] retrospectively reviewed their experience with sacral neuromodulation in ambulatory adult patients with spina bifida and found that it improved urodynamic parameters, urgency-frequency, urinary incontinence, and bowel function. Most of their patients with spina bifida, however, needed computed tomographic guidance for lead placement because of their abnormal sacral anatomy.[48] To further evaluate the efficacy of sacral neuromodulation in patients with neurogenic bladder, Leichti et al[49] conducted a sham-controlled, double-blind, multicenter study that included 3 patients with spina bifida. Most patients in this study, including 2 patients with spina bifida, had more than 50% improvement in bladder diary variables.[49] Based on extrapolation from these small studies, sacral neuromodulation can be added to the armamentarium of surgical options for select patients with spina bifida for whom medical management fails.

BLADDER AUGMENTATION

Bladder augmentation, with or without a concomitant catheterizable channel and bladder neck procedure, remains the recommended treatment for bladder dysfunction when medical management fails. Bladder augmentation has many risks, however, with a reported 44% 10-year risk of reoperation.[50] Although advances in the bladder augmentation procedure have been limited to date, it is possible that the procedure could be improved with tissue engineering in the future. In an effort to circumvent the complications from bladder augmentation with gastrointestinal segments, Joseph et al[51] designed a study in which autologous cell–seeded biodegradable scaffolds were used for bladder tissue regeneration over a 5-year period. Unfortunately, results from phase II trials using engineered bladder tissue have been disappointing. Neither bladder compliance nor bladder capacity was clinically or statistically improved at 12-month or 36-month follow-up.[51] In addition, all participants experienced adverse events, with 4 patients experiencing bowel obstruction or bladder rupture.[51]

Although surgery has been shown to improve urinary continence, enhanced quality of life (QOL) remains debatable. In a study investigating health-related QOL via Quality of Life Assessment in Spina Bifida questionnaires completed by children 8 to 17 years of age with spina bifida, researchers found that urinary incontinence is negatively associated with health-related QOL, with increasing magnitude from ages 10 to 17 years.[52] Researchers found that higher levels of incontinence were associated with lower health-related QOL.[52] In addition, QOL and bladder symptoms have recently been analyzed and compared in patients with spina bifida who catheterize by urethra or catheterizable channel after bladder reconstruction.[53] This cross-sectional analysis at a spina bifida center found that patients catheterizing by channel reported few bladder symptoms, although this finding was not statistically significantly associated with improved overall or bladder-related QOL.[53]

BOWEL MANAGEMENT

Optimization of bladder function must occur simultaneously with optimization of bowel function. If patients have difficulty emptying the rectum, they will experience an increase in bladder overactivity. The Spina Bifida Association recently published guidelines to

standardize bowel management for patients with spina bifida.[54] Bowel management historically involved the use of suppositories, polyethylene glycol 3350, or rectal (antegrade) enemas. One downside of rectal enemas is that patients need assistance to perform them. To address this problem, the Peristeen enema system (Coloplast) was introduced. This transanal irrigation device has been shown to be effective in improving bowel management for individuals with neurogenic bladder and enables the patient to perform enemas independently.[54,55] With personalized training on system use, patients show greater adherence and therefore improved symptoms, well-being, comfort, and self-sufficiency.[56,57] Navina, another transanal irrigation system, has shown similar success to the Peristeen system.[58] By increasing adherence to their bowel regimen, patients should be more likely to experience improvement in bladder overactivity. In addition to improved bowel function, bowel management has the potential to improve QOL. A recent study reported improved QOL, assessed by patients and their parents, in domains such as physical and emotional well-being, self-confidence, family, friends, and daily routine at school.[59]

As advances continue in treatment and outcomes for patients with spina bifida, a newer obstacle to overcome is the availability of and access to transitional care for this population with complex needs. Pediatric multidisciplinary clinics are a gold standard for the treatment of children with spina bifida, but successful transition to adult care remains difficult to achieve.[60] Aging patients have evolving challenges in addition to continence issues, including reproductive system concerns such as sexual function, fertility, and pregnancy; orthopedic concerns; and, ultimately, functional independence and QOL.[60] The Transition Readiness Assessment Questionnaire has been adopted to guide the transition process.[61] Variations of transitional programs have been established at institutions wherein patient readiness is typically assessed at about age 12 to 14 years according to the 2018 guidelines for the care people with spina bifida, individual transition plans are enacted, and the responsibilities for the patient are gradually increased as they switch to adult clinics.[62] A national survey of urologic health care professionals (HCPs) who are members of the Spina Bifida Association Network and American Urological Association Working Group on Urologic Congenitalism identified the top 3 obstacles to successful transition from pediatric clinics as lack of resources to organize and execute a specialized adult-only multidisciplinary clinic, inability to identify adult HCPs to staff the clinic, and the belief that such a clinic is not necessary.[63] The same surveyed population believed that the top resources needed to facilitate transition of care are development of care guidelines, improved HCP collaboration, improved access and advocacy, and development of an advanced training pathway for HCPs.[63] Some headway has been made in safely transitioning pediatric patients to HCPs focusing on adults; however, there is still much work to be done.

Conclusion

The management of pediatric neurogenic bladder for patients with spina bifida has come a long way, and improvements continue to be made, particularly in the prenatal period. As newer medications arrive on the scene and we learn ways to improve patient compliance with studies and treatments, outcomes will continue to improve.

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