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Article *in* Intractable & Rare Diseases Research · January 2021

DOI: 10.5582/irdr.2020.03077

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Advance Publication DOI: 10.5582/irdr.2020.03077

Perspectives on urological care in spina bifida patients

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SUMMARY Spina bifida (SB) is a neurogenetic disorder with a complex etiology that involves genetic and environmental factors. SB can occur in two major forms of open SB or SB aperta and closed SB or SB occulta. Myelomeningocele (MMC), the most common neural tube defects (NTDs), occurs in approximately 1 in 1,000 births. Considering non-genetic factors, diminished folate status is the best-known factor influencing NTD risk. The methylenetetrahydrofolate reductase (MTHFR) gene has been implicated as a risk factor for NTDs. The primary disorder in the pathogenesis of MMC is failed neural tube closure in the embryonic spinal region. The clinical manifestation of SB depends on clinical type and severity. SB can be detected in the second trimester using ultrasound which will reveal specific cranial signs. The management of MMC traditionally involves surgery within 48 h of birth. Prenatal repair of MMC is recommended for fetuses who meet maternal and fetal Management of Myelomeningocele Study (MOMS) specified criteria. Urological manifestations of SB include urinary incontinence, urolithiasis, sexual dysfunction, renal dysfunction, and urinary tract infection. Renal failure is among the most severe complications of SB. The most important role of the urologist is the management of neurogenic bladder. Medical management with clean intermittent catheterization and anticholinergic treatment is generally considered the gold standard of therapy. However, when this therapy fails surgical reconstruction become the only remaining option. This review will summarize the pathogenesis, risk factors, genetic contribution, diagnostic test, and management of SB. Lastly, the urologic outcomes and therapies are reviewed.

Keywords spina bifida, neuropathic bladder, myelomeningocele, urology

1. Introduction

Spina bifida (SB) is the most common birth defect affecting the central nervous system. The most common form of SB is myelomeningocele (MMC). MMC usually affects the brain with characteristic phenotypic features that involve cognition, behavior, and adaptation (*1*). SB is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. EUROCAT, the European network of population-based registries for epidemiological surveillance of congenital anomalies estimated the prevalence (including chromosomally-related disorders) of 'SB' and 'neural tube defects' (NTDs) at 0.51 and 0.94 respectively per 1,000 births, stillbirths and pregnancy terminations (*2*). A study done in Malaysia showed that the prevalence of NTDs was 0.42 per 1,000 live births (*3*). In a systemic review, the overall birth prevalence of NTDs in India was 4.1 per 1,000 (*4*). Data for 2000 to 2014 in five counties in northern China were obtained through a population-based birth defects surveillance system. The prevalence of total NTDs was extremely high from 2000 to 2004, but it began to decrease continuously thereafter, from a peak of 120.0/10,000 in 2004 to a low of 31.5/10,000 in 2014 (*5*). In other areas, the reported NTD prevalence ranges and medians for each region were: African (5.2-75.4; 11.7 per 10,000 births), Eastern Mediterranean (2.1-124.1; 21.9 per 10,000 births) (*6*).

The causes of this disorder are heterogeneous and include chromosome abnormalities, single-gene disorders, and teratogenic exposures. However, the cause is not known in most cases. Up to 70% of SB cases can be prevented by maternal, periconceptional folic acid

supplementation (*7*). Most neurological dysfunctions related to MMC are already well established in adult ages, but new and more debilitating clinical problems can appear. Autonomic dysfunction, particularly from the bladder and bowel, remains a challenge also for persons with SB in adulthood (*8*). MMC management includes life-long comprehensive neurologic, urologic, musculoskeletal, skin, and rehabilitation management (*9*).

Urological manifestation in patients with MMC is common, resulting in serious negative psychological and medical effects. This mandates an early follow-up, and a comprehensive management plan to prevent any irreversible renal damage and stabilize bladder function (*10*). Despite consensus regarding early urological involvement in the care of patients with SB, controversy remains regarding optimal management. Major reconstructive urological surgeries still have a major role in the management of these cases to protect the upper urinary tract and to achieve continence (*11*). The urologist plays an important role in the multidisciplinary team of physicians who provide care for patients with SB. The essential role of the urologist is to prevent deterioration of kidney function and ensuring adequate bladder voiding. To achieve those goals medical and surgical therapies are used such as clean intermittent catheterization (CIC), antimuscarinic and urinary tract reconstruction (*12*).

We performed a narrative review to discuss briefly the etiology, pathophysiology, diagnosis, and treatment of SB. The urologist had a crucial role in the management of patients with SB. Understanding the pathogenesis of SB enables optimization of the management of urologic problems created by this malformation. We reviewed the current literature regarding the urological outcomes and management of patients with SB.

2. Overview of SB

2.1. Pathogenesis

On the basis of the presence or absence of overlying skin covering, spinal dysraphism is divided into open and closed types. In Open spinal dysraphism (OSD) overlying skin covering is absent and the neural elements are exposed to the external environment whereas, in the closed type, the neural elements have a skin covering. OSD results from faulty primary neurulation due to defective closure of the neural tube. About 98.8% of all OSDs are made up of MMC. Other entities of OSD include myelocele and hemimyelocele. Closed spinal dysraphism include meningocele, dermal sinus, and complex dysraphic states (*13*). There are two fundamental theories regarding the embryogenesis of MMC both encompassing a disorder of primary neurulation. In the so-called non-closure theory initially suggested by von Recklinghausen, it is proposed that neural tube defects represent a primary failure of neural tube closure. In the overdistension theory, introduced in 1769 by Morgagni and popularized by Gardner, it is proposed that NTDs arise through overdistension and rupture of a previously closed neural tube. The non-closure theory is more widely accepted and certainly accounts for the majority of human NTDs (*14*).

The neural damage in MMC may be primarily the result of defective spinal cord development, a secondary event resulting from damage to the exposed spinal cord by the intrauterine milieu. The two-hit hypothesis states that primary congenital abnormalities in anatomic development allow a relatively normal spinal cord to become secondarily damaged by amniotic fluid exposure, direct trauma, hydrodynamic pressure, or a combination of these factors (*15*). If the progression of spinal neurulation along the body axis is severely delayed or halted, then open SB results. In normal embryos, the vertebral arches develop from the sclerotomal component of the axial mesoderm, which migrates dorsally to surround the closed neural tube before undergoing cartilaginous and bony differentiation. When the neural folds remain open, the sclerotome is unable to cover the neuroepithelium and a bifid vertebral column is a secondary result (*16*). In summary, the neurologic defects in MMC result from primary incomplete neurulation and secondary chronic prenatal damage to the exposed neural elements through mechanical and chemical trauma (*17*).

Meningocele is often described as a less severe variant of MMC in which the spinal cord is not found in the sac and is described by embryologists to be absent of neural matter in its herniated sac. MMC is usually associated with a type II Chiari hindbrain malformation, ventriculomegaly, and hydrocephalus (*18*). Some structural anomalies are virtually unique to individuals with MMC, including a complex pattern of cerebellar dysplasia known as the Chiari II malformation. Other structural anomalies are not necessarily unique to MMC, including altered development of the corpus callosum and posterior fossa (*19*). The Chiari malformation is associated with hindbrain herniation, which may be caused by low spinal pressure relative to cranial pressure. The relationship between hydrocephalus and SB has been the subject of prolonged debate. A hypothesis proposed in this essay supports the view that SB is a manifestation of progressive hydrocephalus in the fetus. It is proposed that that mesodermal growth insufficiency influences both neural tube closure and central nervous system pressure, leading to dysraphism (*20*). An open neural tube defect allows fluid to escape from the cranial vesicles, altering the intracranial environment and leads to all of the brain changes seen in the Chiari II malformation. Decompression of the intracranial vesicles causes overcrowding, a decrease in the size of the third ventricle, and changes in the fetal skull (*21*). Hydrocephalus usually develops secondary to impaction of the posterior fossa contents on the foramen magnum, leading to occlusion of the outlets of the fourth ventricle

Table 1. Pathogenesis and characteristics of each type of spina bifida

Type of Spina Bifida	Characteristics	Pathogenesis
Myelomeningocele	Spinal cord is not found in the sac	Non closure theory: Primary failure of neural tube closure.
Meningocele	Neural matter herniating at the site of the lesion	Overdistension theory: Overdistension and rupture of a previously closed neural tube.
Spina bifida occulta	Site of the lesion is covered with skin	Defective secondary neurulation.

Table 2. Risk factors for spina bifida

Maternal factors
Not taking folic acid supplements
Spina bifida patients within third-degree relatives
Antiepileptic drugs
Pregestational diabetes
Gestational diabetes
Obesity
Vitamin B_{12} deficiency
Other factors
Low birth weight in the newborn
Pesticides
Paternal exposure to Agent Orange

with cerebrospinal fluid outflow blocked, or impaired, at the foramina of Luschka and Magendie and resulting in progressive ventriculomegaly. Although there are several theories, it has been demonstrated that 80-90% of children born with MMC are affected with Chiari II malformation, aqueductal stenosis, or fourth ventricular outflow obstruction causing non-communicating hydrocephalus (*22*).

A high number of patients with MMC also suffer from spinal cord tethering (SCT), which progressively worsens neurological function and frequently requires surgical correction (*23*). Approximately 10 to 30% of children will develop SCT following repair of a MMC. Because essentially all children with repaired MMC will have a SCT, as demonstrated on Magnetic resonance imaging (MRI), the diagnosis of tethered cord syndrome (TCS) is made based on clinical criteria (*24*).

There is also a less well-defined group of closed spinal NTDs in which the vertebral arches are malformed but covered by skin. These conditions, including SB occulta and spinal dysraphisms, vary widely in clinical presentation. The more severe subtypes are associated with various abnormalities of the spinal cord, lipoma, and/or anorectal abnormalities (*25*). SB occulta has an overall prevalence of 12.4% in a large, diverse population. SB occulta is more common in men and decreases in prevalence with increasing age (*26*). Closed spinal dysraphism, SB occulta, refers to skin-covered lesions. The cutaneous stigmata that may indicate an underlying dysraphism are particularly hairy patches, subcutaneous lipomas, capillary hemangiomas, dorsal dermal sinuses, and sacral cutaneous pits (*27*). The pathogenesis and the characteristics of each type of SB are summarized in Table 1.

A routine screening for other malformations especially facial clefts, musculoskeletal, renal and cardiac anomalies may need to be considered in infants with NTDs, and genetic counseling seems warranted in most of these complicated cases (*28*).

2.2. Risk factors

Many factors determining SB risks were cited in a comprehension overview, which included third pregnancy, miscarriage, high emotional stress during pregnancy, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes) infection when pregnant, poor housing and maternal age (*29*). Risk factors for SB are summarized in Table 2.

In a study, four variables were significantly associated with the increased risk of having newborns afflicted with SB: not taking folic acid supplements, presence of SB patients within third-degree relatives, taking anti-epileptic drugs without folic acid, and low birth weight in the newborns ≤ 2,500 grams (*30*). Other factors are known or highly suspected to increase the risk for NTDs, including female infant sex and family history of NTDs, as well as maternal Hispanic ethnicity, obesity, pregestational diabetes, gestational diabetes, and hot tub or sauna use (*31*). Folic acid not only prevents the occurrence of a significant proportion of NTDs, but might also decrease the severity of NTDs as long as supplementation is started before conception (*32*).

Currently, strong evidence exists to suggest a causal association for maternal obesity before pregnancy, and paternal exposure to Agent Orange in patients with SB (*33*). Other risk factors for NTD are exposure to certain medications (valproic acid), and vitamin B_{12} deficiency. It was recommended that all women of childbearing age capable of becoming pregnant consume 400 micrograms of folic acid daily to prevent NTD's (*34*). NTDs are a complex disease impacted by genetic susceptibility, epigenetic influences, and environmental insults. Tools are now available to identify genetic contributions in humans using unbiased methods to evaluate the genome and epigenome (*35*).

2.3. Genetic contribution to SB

Disturbance of any of the sequential events of embryonic neurulation produces NTDs, with the phenotype (anencephaly, SB) varying depending on the region of the neural tube that remains open. While mutation of > 200 genes is known to cause NTDs in mice, the pattern of occurrence in humans suggests a

multifactorial polygenic or oligogenic etiology (*36*). The genes contributing to the etiology of NTDs are unknown. Mutations in planar cell polarity (PCP) genes in mice cause a variety of defects including the NTD, craniorachischisis, and sometimes SB. Recent studies have sought rare predicted-to-be-deleterious alterations (putative mutations) in the coding sequence of PCP genes in human cases with various anomalies of the neural tube. PCP rare putative mutations had a weaker role in MMC, being found in approximately 6% of cases and cumulated across CELSR1, FUZ, FZD6, PRICKLE1, VANGL1, and VANGL2 (*37*). Genetic variation might interact in a digenic fashion to generate visible NTD phenotypes and emphasize the importance of these genetic interactions in the development of NTDs in humans (*38*). The Wnt/PCP pathway remains a genetic hotspot. Addressing these issues is essential for understanding the genetic etiology of human NTDs. Data indicate rare damaging variants of the CELSR genes, identified in ~14% of NTD cases, and are expected to be driver genes in the Wnt/PCP pathway (*39*).

Several studies have found a positive association between NTDs and the common mutation 677C > T of 5,10-methylenetetrahydrofolate reductase (MTHFR), and others that have not indicated such an association (*40*). The enzyme MTHFR plays a key role in the folate metabolism pathway and regulates the intracellular folate pool for synthesis and methylation of DNA. The MTHFR gene is located at chromosome 1p36.3. It is assumed that MTHFR genetic polymorphisms play an important role in the development of NTDs; however, only 13% of NTDs were attributed to the MTHFR C677T mutation suggesting that the MTHFR C677T polymorphism alone cannot be responsible for NTDs (*41*). The combination of MTHFR and cystathione-b-synthase (CBS) mutations was reported to have a fivefold increase in the risk for SB compared with each variant alone, indicating the presence of gene-gene interactions (*42*). Another single nucleotide polymorphism (SNP) in the *MTHFR* gene, A1298C, has also been described and studied for its relationship to NTDs. Available data suggest that the A1298C variant alone is probably not a major risk factor for MMC. Data also suggest that compound heterozygosity for the C677T and A1298C alleles might be associated with an increased risk for MMC (*43*). Significant association of SNP (rs3737965) in MTHFR was found. *MTHFR* rs3737965 is located in the promoter sequence and therefore variants may affect transcriptional activity. This SNP was found to be associated with SB risk (*44*).

The identification of genetic risk factors for human NTDs is complicated by the multiplicity of genes participating in neurulation, and the importance of gene-environment interactions. Gene-environment interactions appear likely to contribute to NTD predisposition, with examples including interactions of MTHFR with multivitamin use, methionine synthase reductase (MTRR) with vitamin B_{12} and platelet derived growth factor receptor alpha (PDGFRA) with inositol and zinc (*45*).

2.4. Diagnostic test for SB

Prenatal screening for neurological abnormalities is based on an ultrasound performed routinely or oriented by maternal Alpha Feto Protein (AFP) screening. It should be performed around 12, 22, and 32 weeks. Maternal serum screening can detect up to 80% of cases of SB (*46*). Standard ultrasound improved NTD detection over AFP screening alone, by improving AFP test sensitivity and identifying NTDs in low-risk pregnancies (*47*). Compared with maternal serum AFP performed alone for screening, routine second-trimester ultrasonography was more likely to discover a NTD (*48*). Ultrasound-detectable signs of open SB include "banana sign" of the cerebellum and "lemon sign" of the frontal skull. A chromosomal abnormality was found in 10.9% of isolated SB, which is comparable to the rates reported in similar studies. This suggests that there is a high risk of chromosomal anomalies in these pregnancies compared with normal-appearing fetuses (*49*).

Ultrasound examination is the gold standard for the diagnosis of SB aperta. It represents the main imaging tool used to ascertain this diagnosis early in gestation. Three-dimensional ultrasound is necessary to detect the level and size of the defect. MRI represents a more sensitive tool, giving specific information on the defect and associated anomalies, playing an important role in ruling out the differential diagnosis (*50*). In tertiary fetal medicine centers, two-dimensional and three-dimensional ultrasound allows an accurate determination of the location, type, extent, and upper level of the spinal defect as well as the presence of associated anomalies. Fetal MRI should be restricted to candidates for intrauterine surgery as part of the preoperative protocol (*51*). Fetal MRI has advanced rapidly in the last 25 years, developing from an experimental technique to become a fundamental tool in normal clinical practice in many centers around the world. MRI's ability to detect complex anomalies that involve different organs has been widely reported (*52*).

During the prenatal evaluation, detailed ultrasonographic assessment of the entire spine with the identification of the position and morphology of the conus medullaris and absence of cranial signs of spinal dysraphism are the most valuable sonographic clues for diagnosis of closed SB (*53*). Additional imaging in the postnatal period can be useful in evaluating the newborn with vertebral anomalies noted on prenatal imaging. Plain radiographs (anteroposterior and lateral of the entire spine including the ribs), should be obtained early, optimally in the first 2 months, as the bony

details of a prenatally-noted anomaly are more evident before further ossification of the vertebra. Neonatal spinal ultrasound performed before extensive laminar ossification has occurred (6-12 weeks) will show major intraspinal anomalies and tethering. Evaluation of the neonatal spine is typically performed with ultrasound and radiography, though MRI sometimes plays a role as well (*54*).

Pediatric spinal dysraphism and associated malformations are accurately diagnosed on an MRI scan. MR myelographic 3D-HASTE and STIR sequences should be a part of the protocol to evaluate spinal dysraphism (*55*). Conventional supine MRI findings may include a low-lying conus medullaris, thickened or fat-infiltrated filum terminale, or lipoma; however, imaging sensitivity and specificity for tethered cord can be low. Prone imaging is found to be a sensitive and specific tool, it may have a role as supportive evidence in the diagnosis of tethered and retethered spinal cord (*56*). New dynamic MRI-based parameters to establish the presence and magnitude of TCS have been defined (*57*).

2.5. Management of SB

Medical management of a child with MMC requires a lifelong multidisciplinary effort including urology, physical orthopedics, and social therapy besides neurosurgery. The initial and probably the most crucial step begins with proper repair of the lesion (*58*). The recommended standard of treatment for open presentations of SB is prenatal surgical repair or postnatal repair within the first few days of life. Prompt postnatal repair has been associated with reduced risk of ventriculoperitoneal (VP) shunt infection, neurogenic bladder (NB), and neurodevelopmental delays (*59*). Early surgical correction of MMC-related spinal deformities improves body balance and quality of life. The dual growing rod technique is safe and effective in cases of moderate neuromuscular spinal deformities at an early age (*60*). The subtraction (decancellation) vertebrectomy technique with preservation of the dural sac is a safe and efficacious technique for correction and stabilization of MMC- kyphosis in young patients. Morbidity is reduced, as compared with excision techniques (*61*).

Symptomatic hydrocephalus is a common condition associated with MMC. Traditionally, hydrocephalus was treated with insertion of a VP shunt. Endoscopic third ventriculostomy (ETV) with choroid plexus cauterization (CPC) and conservative management of relatively stable ventriculomegaly are alternatives to VP shunt placement (*62*). From 1998 to 2014, hydrocephalus treatment has become delayed more and the number of hydrocephalic MMC patients not treated on initial inpatient stay has increased. A meta-analysis demonstrated that shunt malfunction and infection rates do not differ between delayed and simultaneous hydrocephalus treatment (*63*). ETV/CPC is a feasible alternative to ETV and VP shunt in infants with hydrocephalus (*64*).

The Myelomeningocele Study (MOMS trial) was published, demonstrating a decreased need for shunting, a reversal of hindbrain herniation, and better neurologic function in the prenatal repair group compared to postnatal repair with maternal complications and prematurity as a trade-off (*65*). Class I evidence from 1 study and class III evidence from 2 studies suggest that, in comparison to postnatal repair, prenatal surgery for MMC reduces the risk of developing shunt-dependent hydrocephalus. Therefore, prenatal repair of MMC is recommended for those fetuses who meet specific criteria for prenatal surgery to reduce the risk of developing shunt-dependent hydrocephalus (*66*). Despite the confirmed benefits of prenatal surgery, considerable maternal and fetal risk exists compared with postnatal repair. Early gestational age at surgery and development of chorioamniotic membrane separation are risk factors for ruptured membranes (*67*).

Most centers offering open fetal surgery for SB use the MOMS trial criteria to determine eligibility for surgery; some also consider women with a body mass index of 40, those with well controlled insulin dependent diabetes or those who have previously undergone a lower segment cesarean section. In line with the evidence discussed, surgery is typically planned to take place between 23^{+0} and 25^{+6} weeks of gestation (*68*). Maternal obstetric outcomes are superior for fetoscopic SB repair compared to open fetal surgery and avoids the ongoing risk in a future pregnancy. Neonatal and infant benefits appear equivalent (*69*).

Infants with classic cutaneous markers of occult spinal dysraphism, with progressive neurologic, skeletal, and/or urologic findings, present no diagnostic or therapeutic dilemma: they routinely undergo MRI and spinal cord untethering (SCU). Conversely, in asymptomatic patients or those with fixed, minor abnormalities, the risk profile of these occult SB cohorts should be carefully considered before SCU is performed (*70*). Untethering should be performed immediately once the patient shows evidence of symptomatic lumbosacral cord tethering, irrespective of age. Untethering can interrupt the progression of symptoms, but sphincter dysfunction and muscle weakness are more likely to improve or resolve (*71*). However, neurologic recovery with regard to pain and neurologic deficit shows great variation, with improvement rates ranging from 0 to 100%. The causes of tethering, preoperative duration of symptoms, and completeness of untethering could cause the outcomes to vary (*72*). Spine-shortening osteotomy successfully helps to reduce the spinal cord tension without causing direct neural damage. At a minimum, it stabilizes the patients' symptoms and/or helps delay neurological

deterioration for a period of time (*73*). Spine-shortening osteotomy is a safe and effective technique for TCS patients, especially in more challenging cases, such as complex malformations or revision surgery (*74*).

3. Urologic outcomes of SB

Urological manifestations of spinal dysraphism can include increased risks of urinary incontinence, urinary tract infection, urinary calculi, sexual dysfunction, end-stage renal disease, and iatrogenic metabolic disturbances (*75*). Congenital closed spinal anomalies are associated with distortion of the spinal cord, the spinal nerve roots, or both, and can result in neurological abnormalities of the lower limbs and neuropathic bladder dysfunction. All patients with a known or suspected diagnosis of closed SB should have a videourodynamic assessment (*76*).

A study was conducted by Sakakibara *et al.* to assess the urologic and neurologic outcomes in patients diagnosed with SB cystica and occulta. They performed a neurological examination, urinary questionnaire, and urodynamic studies in 28 consecutive patients with urinary symptoms, including 16 with the cystic form, all of whom underwent neonatal surgical management, and 12 with the occult form who did not undergo surgery. Urinary incontinence and enuresis were common at all ages, and large post-micturition residuals and vesicoureteral reflux were not uncommon, particularly in the cystic form. Bladder abnormalities in the cystic and occult forms included detrusor hyperreflexia during filling in 38% and 42%, low compliance detrusor in 81% and 67%, supersensitivity to bethanechol in two (100%) patients with the cystic form and in three of four (75%) with the occult form, and impaired bladder sensation in 25% and 8% in each form, respectively (*77*). Summers *et al.* retrospectively reviewed patients seen at adult dedicated SB clinics at the universities of Utah and Minnesota from April 2011 to April 2012. They identified 65 patients from these clinics with SB. Fifty-five patients (85%) reported a urologic problem at the time of their visit. Urinary incontinence was most common in 34 (52%), followed by recurrent urinary tract infection in 22 (34%), catheterization troubles in 8 (12%), and calculi in 6 (9%). Sixty-three patients (97%) required some sort of intervention. Patients had many active urologic problems and operative management was often needed (*78*).

Bladder dysfunction in SB patients can lead to significant morbidity due to renal insufficiency. Vesicoureteral reflux may occur in up to 40% of children with SB by age 5, and up to 61% of young adults with SB experience urinary incontinence (*79*). In SB, the natural history of the urinary tract in untreated NB and sphincter dysfunction is a progressive deterioration by the age of 3 years in up to 58% of patients. Several reports have shown this deterioration to be directly related to increased intravesical pressure. Without proper management, urinary tract infections and elevated bladder pressures with secondary bladder-wall changes may cause upper urinary tract deterioration (*80*).

4. Urologic Management of SB

Children with MMC can be categorized into high and low- risk groups for secondary damage from a NB based on intravesical pressure. Those with elevated pressure are at risk for hydronephrosis or reflux. Evidence suggests that early management of high pressure protects the bladder from additional damage, reducing the need for augmentation (*81*). Treatment for a child with NB is usually conservative and focuses on achieving safe bladder pressures during storage with reliable emptying, *via* voiding or catheterization. The two most important forms of conservative treatment are CIC and pharmacological treatment of functional disorders. Pharmacologic therapy used for NB are anticholinergic drugs, with the most prescribed antimuscarinic drug as first-line therapy of detrusor overactivity (DO) in children being oxybutynin followed by tolterodine, trospium, solifenacin, and darifenacin (*82*).

In SB patients, it is important to realize that after the closure of the back, pelvic floor behavior can change from paralyzed to overactive in the first 2-3 months of life. That is a reason to delay the first urodynamic study until 2 months after birth. Oxybutynin is best started together with CIC immediately after closure of the back. Repeated injection therapy of the bladder with 300 U of botulinum toxin can be an alternative to antimuscarinic therapy. This therapy effectively suppresses detrusor contractions for 6-9 months. Injections need to be repeated at a 6- to 9-month interval (*83*).

When medical and intravesical options fail to provide satisfactory results, surgical reconstruction may be required to maintain low intravesical storage pressure and achieve treatment goals for urinary continence. Current options for surgical management include incontinent diversion for those who are not candidates for CIC or individualized combinations of augmentation cystoplasty, a bladder outlet procedure, and the creation of a catheterizable channel (*84*). Surgical intervention for patients diagnosed with SB is indicated for those at risk for renal deterioration and/or is considered for children who fail to achieve satisfactory continence with medical management. Traditionally surgery concentrates on the bladder and bladder neck, and creation of catheterizable channels. For those with a hostile bladder, enterocystoplasty remains the gold standard for bladder augmentation, although the use of bowel for augmentation remains suboptimal due to secondary complications, including increased risk of infections, metabolic abnormalities, neoplastic transformation and risk of life-threatening perforation (*11*).

As the child approaches the age of five years, continence becomes an increasing concern. Some patients will be continent between catheterization so no

further intervention is necessary. If maximal medical management remains inadequate, surgical options may be entertained. Adolescence can be a difficult time for these patients. Their medical challenges can take an emotional toll and the social consequences of their mobility, cognitive, and continence can be devastating. The improved care of these patients has resulted in a drastic increase in life expectancy. Although surgical intervention is very prevalent at this age, endoscopic revisions to continent diversions and bladder stones account for a majority of the cases during adulthood (*85*).

Urinary tract calculi remain a large source of morbidity for patients with congenital neuropathic bladder. Patients with NB have a 50% incidence of urinary calculi over 10 years. As with patients without NB, the main strategies to prevent stones typically involve increased fluid intake (*86*). In SB cases, renal function may begin/continue to deteriorate into adulthood, becoming the leading cause of adult death. This is thought to occur because of changes in the adult bladder, with increases in storage pressure. Despite being invalidated in the follow-up of adult SB patient's annual serum creatinine, ultrasound and urodynamics are currently the best tools available (*87*).

The transition from a well-known and trusted pediatric clinic to an unfamiliar adult clinic can be difficult, and the ideal protocol for transition or establishment of care in an adult SB clinic is not clearly defined or standardized. Most adult SB patients continue on anticholinergic medications and CIC. A large percentage of patients require urologic procedures in adulthood (*88*). Potential solutions to improve the urologic care of SB patients suggest additional national provider resources, standardized guidelines, multidisciplinary collaboration, access to care, and an advanced-training pathway to improve the care of adult patients with SB (*89*).

Despite having intact neurological control over erection and ejaculation, other physical limitations and social barriers may hinder sexual intercourse and contribute to infertility in SB men. Urinary incontinence is another source of embarrassment that may contribute to social and performance anxiety when it comes to sexual interactions. Infertility in this population can be caused by problems of sperm transport or defects in spermatogenesis (*90*). In general, adult males with SB have normal sexual desires and an interest in addressing these issues with healthcare providers. 75% of men achieve erections, but maintaining erections is a problem and some may be merely reflexive in nature. Many of these men show marked improvement with sildenafil. In SB patients, the erectile dysfunction and infertility are related to the level of neurological lesion with the best performance status in those with sacral lesions and intact reflexes (*91*).

Deterioration of the bladder is not uncommon in patients with TCS. Although the mechanism of this deterioration has not been elucidated, chronic overdistension of the bladder, is associated with infravesical obstruction (due to detrusor sphincter dyssynergia) and persistent DO. Since TCS-associated urological deterioration can occur at any time during follow-up, urologists should be responsible for examining these patients at regular intervals (*92*). In a study, it was concluded that tethered cord release was beneficial in terms of clinical and urodynamic outcomes. Patients with abnormal urodynamics had a 48% improvement after a tethered cord release. Neurogenic DO seems to respond better with a 59% improvement in urodynamics (*93*). Another study conducted by Abrahamsson *et al.* assessed the urodynamic findings in children with MMC after untethering of the spinal cord. After untethering secondary to MMC, 35% of the patients experienced improved bladder function and 5% deteriorated (*94*). In another study, it was demonstrated that a neurosurgical correction after the appearance of an upper motor neuron sign restored normal neurologic and urinary function in all children; and untethering in children presenting at birth with upper motor neuron symptoms resulted in a poorer outcome (*95*). Table 3 summarizes the available options to manage urological problems in SB patients.

Table 3. Urological management of spina bifida

Medical therapy
Antimuscarinic drugs
Surgical options
Augmentation cystoplasty
Urinary diversion
Bladder neck reconstruction
Catheterizable channels
Other options
Clean intermittent catheterization (CIC)
Intravesical botulinum toxin injections

5. Conclusion

SB is a rare congenital spinal anomaly comprising an open form, which appears in infancy, and an occult form, which appears in late childhood and adulthood. Medical management of a child with MMC requires a multidisciplinary approach including neurosurgeon, urologist, and orthopedist. With urologic management, preservation of kidney function, and continence can be achievable for most SB patients. Children with NB require an intensive lifelong therapy.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received July 7, 2020; Revised October 4, 2020; Accepted December 12, 2020.

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Released online in J-STAGE as advance publication January 17, 2021.