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Review / Derleme

Contemporary Urological Management of Spina Bifida

Spina Bifidanın Güncel Ürolojik Yönetimi

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ABSTRACT

Spina bifida is a serious health care problem with life long disabilities and it is also the most common cause of neuropathic bladder dysfunction in children. Upon recent developments in medical practice, the life expectancy of children with spina bifida has increased. Urological management is one of the main issues in the quality of life and health of these patients. With the understanding of the natural course of the disease, we can set standards in the treatment of the urological complications of the disease. This report summarizes the contemporary urological approach to the children with spina bifida and the problems in the natural course of the disease.

Keywords: Spina bifida, urinary bladder, neuropathic, urodynamics, urology, child

ÖZ

Spina bifida yaşam boyu engelliliğe yol açan ciddi bir sağlık sorunudur ve çocuklarda nöropatik mesane disfonksiyonunun en sık nedenidir. Tıp alanındaki son gelişmelerle, spina bifidalı çocukların yaşam beklentileri artmıştır. Ürolojik sorunlar ve tadavileri bu hastaların sağlığı ve yaşam kalitesini etkileyen faktörlerin en önemlilerindendir. Hastalığın doğal seyrinin anlaşılması ile bu hastalığın ürolojik komplikasyonlarının tedavisi için standartlar geliştirilebilir. Bu derlemede spina bifidalı çocukların güncel ürolojik yönetimi ve hastalığın doğal seyri sırasında yaşanan problemler anlatılmıştır.

Anahtar Kelimeler: Spina bifida, idrar kesesi, nörojenik mesane, ürodinami, üroloji, çocuk

Introduction

Spina bifida is a congenital clinical conditon associated with spinal cord injury starting from early antenatal period. This injury causes motor dysfunction of lower extremities, bladder and bowel dysfunction and other conditions ending with life long disabilities. All these systems are affected at different levels with a normal child at one end of the spectrum and a physically and mentally deformed child at the other end. As a principle and in general, management of these patients are difficult as we are trying to fix a pathology under abnormal physiological and anatomical conditions. The aim of this review is to highlight the causes and management strategies of urological problems starting from early childhood until adolescence in spina bifida.

History

Spina bifida was first defined by Hippocrates. The term spina bifida meaning bifid spine was first used by Nicolaes Tulp in 1632. Nicolaes Tulp is famous for Rembrandt's painting The Anatomy Lesson of Dr. Nicolaes Tulp. The early efforts for the managament of spina bifida were a total disaster. In the 17th and 19th centuries, physicians were giving sclerosing agents into the spinal lesion with an obviously fatal outcome. It wasn't until late 19th century that Bayer first proposed to close the defect with musculocutaneous flaps. Modern understanding of the condition was possible with Prof. Frazier's, a famous American neurosuregon, statement of surgical indications for myelomeningocele closure in 1918.

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With Russell's definition of the mechanism of hydrocephalus in 1935, an era of search for the proper treatment of this condition started and went on for the next 20 years. After the 60's, it was just possible to offer a reasonable survival and quality of life for these patients (1).

From the urological point, the management of urological problems became possible following the improvement of neurosurgical outcomes after the 50's. During this period, the only possible solution was using diapers. In the 60's and early 70's, we see the studies of Durham Smith and the use of urinary diversions and cutaneous ureterostomies in the treatment of the urological complications of spina bifida. The definition of clean and self intermittent catheterization (CIC) in 1971 by Lapides et al. (2) was a real revolution in the management of neuropathic bladder dysfunction. In 1981, McGuire et al. (3) defined the detrimental effects of bladder leak point pressures over 40 cmH_2O on the upper urinary tract, which highlighted the importance of urodynamic studies in the follow-up of these patients (4). In 1984, Bauer et al. (5) defined the detrusor sphincter dyssynergia (DSD), and this was an important contribution as he stated for the first time that DSD is an important risk factor for the deterioration of upper tracts and early CIC should be started to prevent this. The advent of oxybutynin was another important cornerstone in the management of neuropathic bladder dysfunction. This medication was first reported for the treatment of gastrointestinal problems in mid 60's. After its usage in dysmenorrhea and other clinical conditions, Diokno and Lapides (6) reported oxybutynin as a new analgesic and anticholinergic drug in the Journal of Urology in 1972. Later this report was followed by experimental studies on detrusor muscle, and oxybutynin entered the treatment armamentarium of neuropathic bladder dysfunction. Today, CIC and oxybutynin is the classical treatment for neurogenic bladder, secondary to spina bifida.

Pathophysiology

Spina bifida is a neural tube defect causing the exposure of spinal cord starting from antenatal period. This exposure ends up with the spinal cord injury both antenatally and postnatally. In the 2nd antenatal week, the fetus is in trilaminar germinal stage. Epiblast of the embryonic disk differentiates to the ectoderm, mesoderm and endoderm. The spinal cord forms from ectoderm, and the periphery of the spinal canal is formed from mesoderm. During the 3rd week of gestation, the middle segment of ectoderm at the dorsum of the fetus starts to thicken and form the neural plate. The lateral borders of the neural plate rises to form the neural fold. The central portion becomes the neural groove after the formation of the neural fold. Neural folds meet in the middle to form the neural tube, the future spinal cord. This event happens during the 4th week of gestation and is named as primary neurulation. Failure of primary neurilation is the cause of open spina bifida, spina bifida aperta (Figure 1). The formation of distal spinal cord and cauda equina is called secondary neurulation and any defect during this formation ends up with closed spina bifida, spina bifida occulta (Figure 2).

Spinal cord injury is the primary cause of neuropathic dysfunction in spina bifida. In the antenatal period, according to the two hit hypothesis, the first hit comes from the defective vertebral development whereas the second hit comes either from the irritative effect of amniotic fluid or mechanical trauma directly to the spinal cord related with fetal movements (7). As a consequence of this event, leg movements, bladder and gastrointestinal functions are affected in the fetus. In our center we have demonstrated the congenital bladder dysfunction with newborn preoperative urodynamic investigations (8). Urodynamic studies may also define the type of bladder dysfunction in the patient (Table II) (9). In severe form of the disease, foot deformities, kyphoscoliosis, hip deformities can be observed as well. For this reason, fetal repair of spinal defect is considered to be a promising treatment in the prevention of the neurologic complications of spina bifida in the future (10).

Neuropathic bladder dysfunction is the main urological problem in spina bifida. Normal urinary function is defined as safe and continent storage and complete voluntary emptying. Thus, voiding cycle is divided into storage and emptying phases. Both of these phases are controlled by

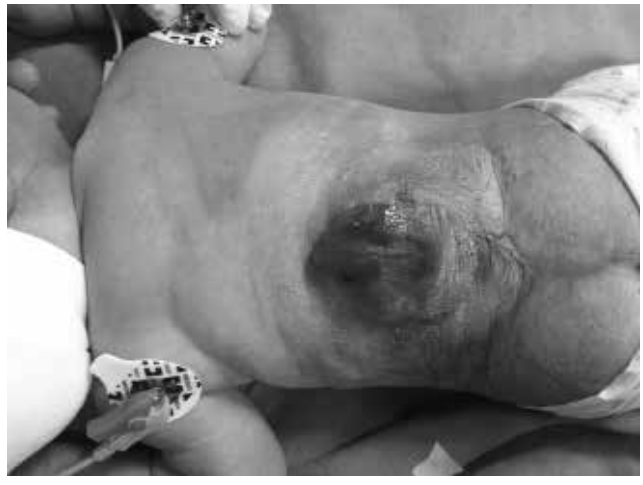

Figure 1. Open spina bifida in a newborn

Table I. Urodynamic results of patients with spina bifida in a study in our center. This table shows the distribution of the bladder dysfunction (24)

n (%)	OAB + DSD	UAB + DSD	OAB	UAB	DSD	UAB + UAS	Normal
SBA (n=275)	137 (49.8%)	45 (16.4%)	26 (9.5%)	2	29 (10.5%)	4	32 (11.6%)
SBO (n=214)	85 (39%)	2	6	9	24 (11.2%)	-	88 (41%)

OAB: Overactive bladder, UAB: Underactive bladder, DSD: Detrusor sphincter dyssynergia, SBA: Spina bifida aperta, SBO: Spina bifida occulta

the nervous system. During the storage phase, afferent sympathetic beta adrenergic activity relaxes detrusor smooth muscle via hypogastric nerve originating from T11-L2 nerve roots, to maintain safe storage pressures in the bladder. This activity causes bladder neck closure with alpha adrenergic activity to avoid urine leakage. When the bladder is full enough for voiding, efferent nerves are stimulated via pelvic plexus to activate parasympathetic activity, which this time causes detrusor contraction and sphincter relaxation for proper emptying. During emptying, striated pelvic muscles also relax voluntarily via the pudental nerve originating from pelvic plexus to support the full emptying of the bladder. We can examine the activity of these nerves with bulbocavernosus reflex which denotes hypogastric nerve activity and anal reflex which shows pelvic plexus activity during physical examination. All these activities are regulated in the locus coeruleus, pontine micturition center in the midbrain. Social continence is also controlled by the inputs from the frontal lobe and all these units maintain voiding activity with the close coordination of higher and lower neurological centers (Figure 3). In spina bifida patients, the innervation of the bladder is affected in almost 90% of the cases. Thus, neuropathic bladder dysfunction is seen as the dyscoordination of the voiding activity. Either detrusor acitivity or sphincter or both of them lose their coordinated action ending with urinary incontinence, recurrent urinary tract infection (UTI), hydronephrosis, vesicoureteral reflux (VUR) and renal scarring with possible future renal function loss. The main aim of the management is to prevent all these complications in these patients (11).

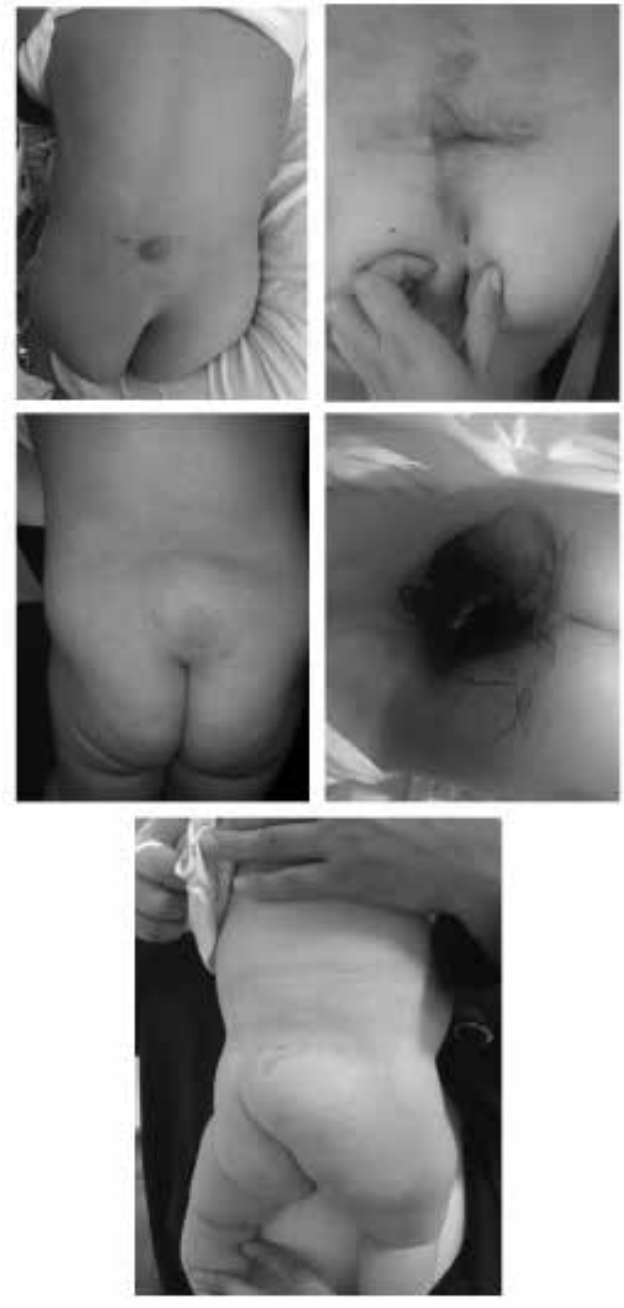

Figure 2. Different appearances of occult spina bifida

Etiology, Clinical Presentation, Diagnosis

Spina bifida is the most common cause of neuropathic bladder dysfunction in children. Teratogenic agents, maternal exposure to heat during gestation, diabetes, folic acid deprivation are thought to be responsible for its etiology. More than 300 genes were studied in spina bifida but the exact genetic mechanism has not yet been identified (12). About 10% of the cases seem to have familial predisposition whereas 90% are sporadic (13). These data show that the causative factors are multifactorial and the exact mechanism still needs to be delineated.

Maternal alpha fetoprotein (AFP) determination is used for antenatal diagnosis. The efficacy of ultrasonography (USG) is limited. However, when AFP determination was used with USG surveillance, the efficacy of the diagnosis was previously found to be 80% sensitive, 99% specific (14).

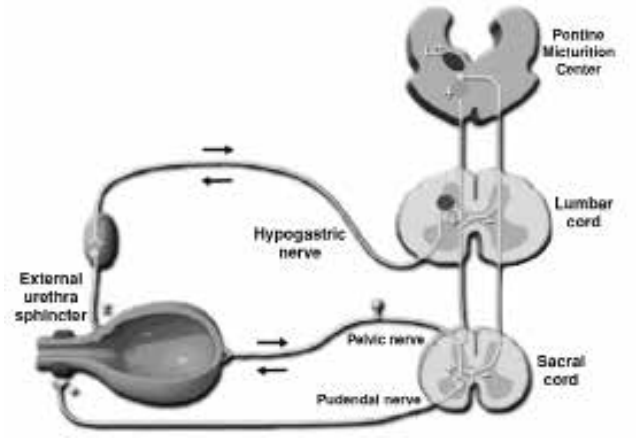

Figure 3. Schematic innervation of bladder

The prevalance of spina bifida was dropped below 1/1000 live birth ratio with folic acid supplementation and the termination of pregnancy in western countries. Prevalance in Turkey was found to be between 1.5-3/1000 births in previous studies (13,15,16). These numbers are important as they show that spina bifida is still a major health problem in Turkey.

After the delivery of the patients, the spinal defect needs to be closed immediately by the neurosurgeons to avoid infection. Initial urological investigations are started after the patient is stabilized. Physical examination, blood urea nitrogen, creatinine determinations and urinalysis are done followed by bladder and renal USG. Initially the baby is observed for urination abilities. If any voiding difficulty is observed, the baby can be started with CIC, proactively. After the closure of the spinal defect, in the first three months postoperatively, evaluation of the bladder functions can be misleading due to transient iatrogenic effects of the surgery. After the spinal shock period resolves, urodynamic studies should be done to identify the characteristics of the bladder dysfunction (Table I). This is important because the possible risk factors for upper tract deterioration should be identified and certain precautions should be taken before any possible undesirable complications occur. Thus, urodynamic studies are very important in the diagnosis and follow-up of these patients. Dimercaptosuccinic acid (DMSA) scintigraphy is also preferred at about 3 months of age for the determination of any congenital renal anomaly, or to set a reference point for future renal follow up. In previous studies, renal problems were shown to be observed in 10-30% of the cases (17,18). This ratio may increase up to 50% until the age of five. Wu et al. (19) have found hydronephrosis in 28% and vesicoureteral reflux in 21% of their patients. In Ege University experience, the rate of VUR has been found to be 29% in spina bifida patients, most of them having high grade reflux (11). To prevent these complications, in our multidisciplinary spina bifida center, we prefer to do urodynamic study every 6 months after 3 months of age in the first year of life, and once every year after 1 year until 5 years of age, and every 2 years after 5 years until adolescence. USG investigations are preferred every 6 months before 1 year of age and once in a year after this age. DMSA is preferred every 2-3 years. This follow-up is necessary because neuropathy is a dynamic phenomenon in spina bifida. During the development of the child, tethered cord may be observed, which may affect the neurological status of the child. Each investigation should be compared with the previous one for the early detection of this condition. In genitourinary USG, we look for any hydroureteronephrosis, size, position of the kidneys, renal pelvis, proximal and distal ureters and bladder wall thickness, bladder anomaly in both empty and full bladders. If any hydronephrosis is detected, voiding cystourethrography is indicated for the identification of hydronephrosis with or without VUR (Figure 4). DMSA is preferred for the detection of any renal scarring, which is actually the final target of the follow-up. Risk factors for scarring should be identified to take proper precautions and act proactively (20). The main

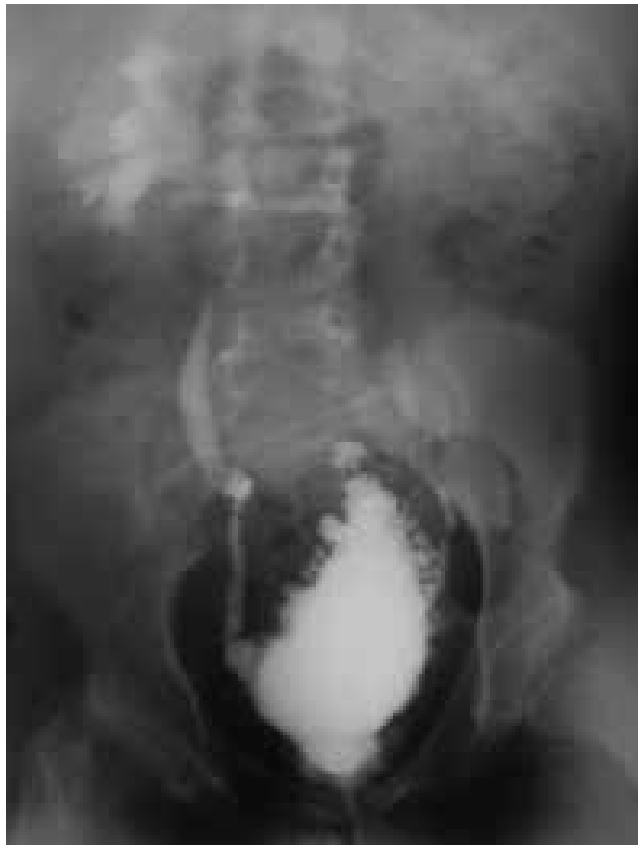

Figure 4. Typical appearance of neuropathic bladder with prominent trabeculations and vesicoureteral reflux

Table II. Common anticholinergics and their doses for children
Oxybutynin (Uropan© 5 mg susp, tab) 0.2-0.4 mg/kg
Tolterodine (Detrusitol©, Toldin©, Toldex©, 1-2 mg tab, 4 mg long acting tab) 2-4 mg/day 2 doses (0.5-2 mg/day)
Propiverine (Mictonorm© 15 mg) 0.5-0.8 mg/kg
Trospium (Spasmex© 15-30 mg tab) 10-25 mg/day 2 doses
Solifenacin (Kinzy©, Natysin©, Solycin©, Vesicare©, Vesifix©, 5-10 mg tab) 5 mg/day single dose (5-10 years of age)
Darifenacin (Emselex©, 7.5-15 mg long acting)
Fesoterodine (Toviaz) 4-8 mg/day

aim of any strategy in the follow-up of a spina bifida patient is to prevent any renal complications.

Treatment

Medical Treatment

The aim of contemporary medical treatment in spina bifida patients is to provide a the safe mechanical emptying of the bladder in children with emptying problems and achieve a safe intravesical pressure in patients with low bladder compliance or high pressures due to overactive bladder dysfunction. In most of the patients, CIC and anticholinergic medications are sufficient to maintain safe storage pressures and capacity with proper bladder dynamics. CIC is important in avoiding the complications of neuropathic bladder dysfunction, and nighttime continuous catheterization may be recommended to those patients who are under increased risk for upper tract changes. In patients who are resistant to anticholinergic treatment, intravesical applications, electrostimulation or neuromodulation may also be added to the treatment regimen. Intravesical Botox© injection is regarded as a second option for a therapy resistant overactive bladder in spina bifida patients. However, its effect disappears after 6-12 months and relaxation is difficult to achieve in noncompliant fibrotic bladders (21).

It can be possible to protect kidney functions and upper urinary tract in 92% of the patients with only anticholinergics and CIC (22).

Oxybutynin is the most common anticholinergic medication used in spina bifida patients and this drug is the only Food and Drug Administration approved medication for children. Anticholinergic treatment may cause some unwanted side effects. After oral oxybutynin, we observed mostly flushing, fever, agitation, skin eruptions in 35% of the patients. The choice of treatment in our center is tolterodine as a second option, but the side effect rate of this medication can be about 17% (23).

The third option can be either trospium or propiverine, depending on the choice of the surgeon. There are also some other ongoing studies for other medications in children (Table II).

Another issue in spina bifida patients is the medical treatment of UTI. UTI can be secondary to a urological abnormality either congenital or secondary to neuropathic bladder dysfunction with improper bladder emptying. Constipation in these children may also aggravate these symptoms. If a urological condition like VUR or hydronephrosis accompanies, its surgical treatment should be considered without delay. If the patient can not empty his/her bladder, CIC should be started and treatment of constipation should be done. In continuous incontinent children using diapers, if they are female and constipation accompanies, UTI may be observed even if they start CIC. Local genital cleaning for CIC with antibacterial tissues are recommended in these children. When CIC is started for the first time, antibiotic prophylaxis should be preferred for at least two weeks. Prophylaxis with Amoxicillin, Cotrimoxazole or Nitrofurantoin may be considered in small children under 1 year of age. However, if no UTI has been observed for the last 6 months, prophylaxis should be discontinued and prompt intravenous antibiotheraphy should be considered if symptomatic UTI is diagnosed. In CIC patients, urinalysis abnormalities may be seen due to microtrauma of the urinary tract. Thus, only symptomatic UTI should be an indication for antibiotherapy and in asymptomatic UTI only, the patient should be encouraged to have proper water intake.

Surgical Treatment

Surgical treatment of urological complications are limited to the patients who have breakthrough UTI with upper urinary tract deterioration. Exact indications for surgical interventions are; bladders with high pressure, low compliance and low capacity, upper urinary tract deterioration because of high grade VUR and incontinence after school age due to low sphincter resistance. Although most of the cases can be managed conservatively, some patients may need surgical interventions. Below, major operations and their indications in spina bifida are depicted:

Vesicostomy

This operation may be necessary in small children with high grade VUR and breakthrough UTI and who have incomplete bladder emptying. It can be done as a time saving procedure for definitive treatment to be planned in the future under more suitable conditions. The bladder characteristics are masked and upon closure of vesicostomy, bladder function should be defined with urodynamics and proper treatment should be planned.

Augmentation Cystoplasty

In low compliant, high pressure bladder which has a low capacity, i.e. below 50% of the expected volume, in order to increase the capacity and decrease intravesical pressure, augmentation operations are preferred. Among many techniques, ileocystoplasty is the most preferred method with relatively low complications in comparison to other conduits. In recent years, augmentation cystoplasty rates have shown a tendency to decrease due to significant complications like stone formation, UTI, metabolic changes and malignant transformation in the bladder (11). Increasing bladder volume may also help in decreasing the severity of associating VUR and incontinence due to low sphincteric resistance. Augmentation is reserved for older children who have enough hand dexterity for CIC because the child becomes CIC dependent after this operation. Regular CIC should be done to avoid perforation of the augmented bladder. Besides, the bladder wash out should be done

everyday to clear the mucus produced by the mucosa of the intestinal segment and also to avoid stone formation. After augmentation cystoplasty, regular controls with cystoscopy is recommended to detect early malignant degeneration. This is why the rate of augmentation is limited to about 6% of cases in major centers (11,24).

Antireflux Surgery

VUR is a significant problem in spina bifida. About 29% of patients have this problem (11). The cause of VUR may be either increased bladder pressures or severe trabeculations with bladder diverticula or changed anatomy in ureterovesical junction due to neuropathic bladder dysfunction. Patients generally have breakthrough UTI and if this condition is not treated, it may end up in renal scarring and renal insufficiency. Reflux in spina bifida tends to have a high grade and conservative follow-up is not an option in this clinical condition. If the reflux is low grade, asymptomatic, and the kidney is proven to be safe in older children, conservative treatment may be considered. Subureteric injection can be preferred in the treatment of VUR in neuropathic bladders but it should be known that the success rates are lower than primary VUR and the bladder should be treated before the correction of the reflux. In high grade VUR with recurrence after subureteric injection, open techniques should be considered. In some bladders, due to fibrotic changes and severe trabeculations, intravesical procedures may be difficult to perform and extravesical procedures may be preferred instead.

Incontinence Surgery

Even if all the measures have been taken, some spina bifida patients keep on leaking urine continuosly. In patients on CIC, if the patient is still wet after CIC every three hours, the patient is accepted to be incontinent. Two types of operations are preferred for these patients; those who increase outlet resistance, and leakage of urine is accepted when the bladder is full, and those for whom any leakage is prevented with valve techniques. Avoiding urinary incontinence is the most difficult surgical challenge in spina bifida. The success rates are between 50-60% in most series. In adolescent and adult spina bifida patients, incontinence is the major factor that decreases life quality and the socialization of the patient. If the first attempt is unsuccessful, bladder neck injections can be added to the primary procedure. If success is still not achieved, the last option is to close the bladder neck to avoid incontinence. Careful follow-up is mandatory after bladder neck repairs as upper urinary tract deterioration may be seen when the outlet resistance is increased (11). Patients should be informed of regular and strict CIC to avoid bladder or augmented bladder perforation. These patients should be followed closely for any sign of upper tract deterioration.

Continent Stoma Operations

Continent stomas are recommended to those patients who have difficulty in catheterization. CIC may be difficult in male patients with constipation as the urethral angle decreases in the membraneuos urethra segment and false tracts may appear, which makes catheterization even impossible. In female patients, if the patient is obese, self catheterization may be difficult as the patient may find it impossible to find urethral meatus. After bladder augmentation, CIC becomes an obligation and the treatment strategy should be formed before the operation. In older children, self catheterization becomes an issue that decreases dependence on other care givers. Mobility is an important factor for socialization and this issue is also important for the independence of the patient. In 1980, appendicovesicostomy was introduced by Mitrofanoff (25) in neuropathic bladder dysfunction. Today, appendicovesicostomy is accepted to be the best option for those patients who need alternative ways of self catheterization. For those patients whose appendix is not suitable for this operation, an alternative may be to use intestinal segments for this purpose. Ileovesicostomy is the option for these children. The best stoma should be as short, straightforward and with less sutures as possible. Continent stomas are not free of complications. Stenosis of the cutaneous opening, perforation, peristomal skin excoriations, loosening of the stoma, urinary leakage due to loss of antireflux mechanism at the level of the bladder, and difficulty in catheterization are the main complications seen in these operations (11).

Surgical treatment of conditions in spina bifida is a real surgical challenge. These children may have certain physical problems like obesity, severe scoliosis, immobility and associating health problems, which make surgery more difficult to perform. Surgeons should keep in mind that they perform these interventions under altered anatomy and in some occasions success may be achieved in staged manner. Proper information of the patient and the family on this issue must be affirmed.

Conclusion

Management of spina bifida needs multidisciplinary approach. Urology is the major component of this team. With recent developments in medical practice, life expectancy of patients with spina bifida has increased. This mandates the health professionals to confront new problems. Quality of life issues, sexual health, psychological support of the patients and the families are important issues which we need to focus on in our country. Physical disabilities limit the mobility of these patients. Thus, the main motto of the health service should be to bring the service to the patient, not bringing patient to the service. Spina bifida can be prevented with folic acid supplementation before pregnancy and food fortification. Public health departments should be made aware of this issue, and state policies should be formed for preventive measures. We can increase our

health standards but these patients should be supported psychologically to adapt to social life within the community. Our main goal should be to give them and their parents a hope for their future. We should keep in mind that, they may not be a soccer player or a waiter or a runner but they can be a writer, a poet, a painter, a teacher, a sportsman joining the olympics. We can not accept it for a child to await his/her death in the corner of the house or consider him/her as a burden to the community. They can be an active member of the community who can make their own contribution instead of being considered as a burden. Our duty as health professionals is to provide an organised care for them and inform the community correctly. Maybe the most important contemporary issue in the treatment of spina bifida is to change the paradigm of a fatal condition into a healthy normal life in their own standards.

Ethic

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şeyhmus Kerem Özel, İbrahim Ulman, Concept: Şeyhmus Kerem Özel, İbrahim Ulman, Design: Şeyhmus Kerem Özel, İbrahim Ulman, Data Collection or Processing: Şeyhmus Kerem Özel, Analysis or Interpretation: Şeyhmus Kerem Özel, İbrahim Ulman, Literature Search: Şeyhmus Kerem Özel, İbrahim Ulman, Writing: Şeyhmus Kerem Özel, İbrahim Ulman.

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References

1. Goodrich JT. A Historical Review of the Surgical Treatment of Spina Bifida. In: Özek MM, Cinalli G, Maixner WJ (eds). The Spina Bifida Management and Outcome, Milan, Springer, Verlag Italia, 2008. p. 3-19.
2. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, intermittent self-catheterization in the treatment of urinary tract disease. Trans Am Assoc Genitourin Surg 1971;63:92-6.
3. McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126:205-9.
4. Bauer SB, Austin PF, Rawashdeh YF, et al. International Children's Continence Society's recommendations for initial diagnostic evaluation and follow-up in congenital neuropathic bladder and bowel dysfunction in children. Neurourol Urodyn 2012;31:610-4.
5. Bauer SB, Hallett M, Khoshbin S, et al. Predictive value of urodynamic evaluation in newborns with myelodysplasia. JAMA 1984;252:650-2.
6. Diokno AC, Lapides J. Oxybutynin: a new drug with analgesic and anticholinergic properties. J Urol 1972;108:307-9.
7. Adzick NS. Fetal myelomeningocele: natural history, pathophysiology, and in-utero intervention. Semin Fetal Neonatal Med 2010;15:9-14.
8. Özel ŞK, Alataş İ, Erdoğan T, Tunç T, Alim A, Kara N, Canaz H. Preoperative evaluation of newborns with spina bifida. Turkish National Pediatric Urology Congress 2015.
9. Özel ŞK. Urological and gastrointestinal problems in spina bifida. Turkiye Klinikleri J Orthop&Traumatol-Special Topics 2015;8:33-8.
10. Alataş İ, Canaz H, Özel K, Gedikbaşı A, Kohl T. Repair of spina bifida aperta with percutaneous minimal invasive fetoscopic method: First two cases in Turkey. Perinatoloji Dergisi 2016;24:54-60.
11. Ulman İ. Surgical management of urological complications in spina bifida patients. Turkiye Klinikleri J Pediatr Surg-Special Topics 2016;6:83-8.
12. Saraç M, Özel ŞK, Önalan Etem E, Yüce H, Bakal Ü. Determination of tetrahydrofolate reductase,TEAD 2 and PAX3 gene polymorphisms in patients with spina bifida. Çocuk Cerrahisi Dergisi 2014;28:61-6.
13. Saraç M, Özel ŞK, Kazez A. Spina bifida: The condition in Eastern Anatolia. Çocuk Cerrahisi Dergisi 2007;21:116-9.
14. Kraus SR, Boone TB. Pediatric neurogenic bladder: Etiology and diagnostic evaluation. In: Gonzales ET, Bauer SB (eds). Pediatric Urology Practice, Philadelphia, Lippincott Williams & Wilkins, 1999. p. 365-431.
15. Tuncbilek E, Boduroglu K, Alikasifoglu M. Neural tube defects in Turkey: prevalence, distribution and risk factors. Turk J Pediatr 1999;41:299-305.
16. Mandıracıoğlu A, Ulman İ, Lüleci E, Ulman C. The incidence and risk factors of neural tube defects in İzmir, Turkey: a nested case-control study. Turk J Pediatr 2004;46:216-20.
17. Bauer SB. Early evaluation and management of children with spina bifida. In: King LR (ed). Urologic Surgery: Neonates and Young Infant, Philadelphia, WB Saunders, 1988. p. 399.
18. Chiaramonte RM, Horowitz EM, Kaplan GW, Brock WA. Implications of hydronephrosis in the newborn with myelodysplasia. J Urol 1986;136:427-9.
19. Wu HY, Baskin LS, Kogan BA. Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. J Urol 1997;157:2295-7.
20. Ozel SK, Dokumcu Z, Akyildiz C, Avanoglu A, Ulman I. Factors affecting renal scar development in children with spina bifida. Urol Int 2007;79:133-6.
21. Tiryaki S, Yagmur I, Parlar Y, et al. Botulinum injection is useless on fibrotic neuropathic bladders. J Pediatr Urol 2015;11:27.
22. Kasabian NG, Bauer SB, Dyro FM, Colodny AH, Mandell J, Retik AB. The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration. Am J Dis Child 1992;146:840-3.
23. Özel ŞK, Alataş İ, Tunç T, Alim A, Canaz H. Side effect profile of anticholinergic drugs in the treatment of neuropathic bladder dysfunction in children: A clinical study. 5th ed. Turkish National Pediatric Urology Congress, Antalya, 16-19 April 2014.
24. Lendvay TS, Cowan CA, Mitchell MM, Joyner BD, Grady RW. Augmentation cystoplasty rates at children's hospitals in the United States: a pediatric health information system database study. J Urol 2006;176:1716-20.
25. Mitrofanoff P. [Trans-appendicular continent cystostomy in the management of the neurogenic bladder]. Chir Pediatr 1980;21:297-305.