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Complications of untreated and ineffectively treated neurogenic bladder dysfunctions in children: our own practical classification

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Abstract. – The neurogenic dysfunctions of the detrusor and the sphincter are caused by either a known congenital defect of the nervous system or by acquired damage to the nervous system. In patients with idiopathic bladder dysfunctions neurological examinations fail to reveal any pathology in the nervous system.

The treatment strategy for the patient with detrusor-sphincter dysfunction should be based on a comprehensive functional and morphological evaluation.

Clean Intermittent Catheterization is mandatory if voiding is ineffective. Reduced bladder capacity related to detrusor overactivity and decreased bladder walls compliance is successfully managed conservatively with oral anticholinergics. Conservative treatment prevents complications in the majority of patients.

However, despite proper conservative treatment, some patients still develop complications.

We propose our own practical classification of complications characteristic for the bladder and sphincter dysfunctions: 1. Urinary tract infections; 2. Urolithiasis; 3. Anatomic changes in the lower urinary tract; 4. Anatomic changes in the upper urinary tract; 5. Functional disturbances of kidneys parenchyma; 6. Urinary incontinence.

Proposed practical classification of complications of bladder and sphincter dysfunctions is clear and simple. This classification can be used both in children with neurogenic and non-neurogenic dysfunctions. It is helpful in planning follow-up procedures and evaluation of treatment results.

Key Words:
Neurogenic bladder, Urinary incontinence, Complications, Child.

Introduction

The organs of the urinary system are traditionally classified as belonging to the upper or the lower urinary tract. The lower urinary tract (LUT) anatomically comprises the bladder and urethral sphincters, which together form one operating unit. Due to the specificity of the performed action, part of the bladder dome is known as the detrusor, and the sphincters are classified into the internal and the external one.

However, for practical reasons, we normally simplify the issue and talk about functional disorders of the LUT, i.e. detrusor-sphincter dysfunctions, also referred to in short as bladder dysfunctions.

The distinction still holds between neurogenic bladder dysfunctions (NBD) and non-neurogenic (idiopathic) bladder dysfunctions (IBO). In patients with NBD, i.e. those having the neurogenic bladder, dysfunctions of the detrusor and the sphincter complex are caused by either a known congenital defect of the nervous system or by acquired, post-traumatic, post-inflammatory or neoplastic damage to the nervous system. In patients with non-neurogenic (idiopathic) bladder dysfunctions neurological examinations fail to reveal any pathology in the nervous system[1,2].

In the developmental age, dysraphic malformations are the most common causes of NBD. That group is characterized by a considerable variety of clinical manifestations, from occult spinal dysraphism, non-symphysis of single lumbar vertebral arches to extensive open meningomyeloceles reaching the thoracic region with co-existing hydrocephalus. The type of detected urinary tract dysfunction is not clearly linked to the defect morphology (open, closed), the level of dysraphism or the extensiveness of the cleft. Children with the so-called occult spinal dysraphism form a specific group of patients in which the progressing damage of the nervous system may initially manifest itself solely in bladder dysfunction with gradually increasing incontinence.

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Other, more rarely encountered causes of NBD in children include: sacral agenesis, hydrocephalus, neoplastic tumours of the central nervous system, particularly sacro-coccygeal ones, post-inflammatory or post-traumatic lesions of the spinal cord, cerebral palsy and developmental defects of the small pelvis organs (imperforate anus)[3-5].

The symptoms reported by patients to a paediatrician or an urologist are urinary tract infection and incontinence (daytime urine incontinence and nocturnal enuresis). Sometimes the patient is referred to the specialist as a result of an ultrasonographic examination that has revealed certain abnormalities such as thickening of the bladder wall, various degrees of residual urine after micturition, dilatation of the ureters or the renal collecting systems[2,6].

The treatment strategy for the patient with a neurogenic detrusor-sphincter dysfunction should be based on a comprehensive functional and morphological evaluation. That evaluation is based on the results of performed diagnostic tests individually chosen for the patient depending on detected pathology.

Usually, such tests are performed in a certain sequence, beginning from the urinalysis and urine culture through biochemical tests, the analysis of the morphology of the urinary tract (ultrasonography, cystography, renal scans, intravenous pielography, computer tomography) up to the evaluation of the bladder and sphincter functions in urodynamic testing. Urodynamic evaluations make it possible to describe bladder dysfunctions and the dysfunctions of the urethral sphincters, while the other tests are used to evaluate the type and severity of complications caused by the urinary system dysfunctions[3].

The correct functioning of the bladder-sphincter unit is manifested by periodic, controlled urination in portions adequate to the patient's age with continence maintained between particular acts of micturition.

The evaluation of the bladder function in older children should begin with keeping for at least three consecutive days of a Voiding Diary, also known as 'Frequency/Volume Chart'. It contains data on the hours and volumes of passed or catheterized urine. On the basis of that chart/diary we are able to establish the three most important parameters: the number of micturitions per 24 hours, the maximum volume of the urine passed testifying to the anatomical capacity of the bladder, and the functional bladder capacity – an average voided volume.

An adult should pass urine every 3-4 hours in portions of 400-600 ml.

Literature offers various formulas for the calculation of age-related bladder capacity for children. The results obtained with the use of those various formulas are similar. The most frequently used is Hjälmås formula: Expected Bladder Capacity (EBC): volume (ml) = 30 × age (in years) + 30[7-9].

The Practical Division of Urination Problems

Analysing the data obtained from the diary, we may identify three groups of patients:

1. Those with normal/correct bladder function,
2. Those with urination irregularities, and
3. Those who have lost control over their bladder and do not urinate at all.

Ad 1. The correct condition: regular urination, fully controlled by the patient, in portions adequate to age, without complaints.

Ad 2. The child passes urine periodically but the volumes are not correct:

A) Frequent passing of urine in decreased volumes: more than 8 times per 24 hrs, vol < 65% EBC, (*OAB* = overactive bladder syndrome) with frequency and urgency symptoms;

B) Sporadic passing of large portions of urine vol > 150% EBC, (LBS = Lazy Bladder Syndrome), voiding postponements;

C) Irregular miction characterized by considerable differences in the volume of the passed urine, which commonly is connected with various degrees of residual urine after miction.

Each of the above-described conditions may be accompanied with additional symptoms, such as: symptoms of dysuria, urine incontinence, infection of the urinary tract.

Ad 3. Total lack of control over passed urine. In children with dysraphic malformations, the fibres of the efferent and afferent, motor and sensory pathways and spinal centers responsible for controlling bladder and sphincters functions are seriously damaged. In children who have no sensation of bladder fullness and lack the urethra sensation or in whom that sensation is considerably decreased we observe the inability to pass urine in a voluntary, controlled manner; the result is uncontrolled urine leaking characteristic for severe cases of the NBD.

Having the data from the Voiding Diary, we may perform urodynamic tests in a reliable manner. We begin with the performance of the simplest urodynamic test, i.e. uroflowmetry. In order to obtain the complete picture of the miction effectiveness, ultrasonographic evaluation of the quantity of urine remaining in the bladder after urination is always necessary. Uroflowmetry is a non-invasive test evaluating the function of the urinary system in the voiding phase. More complicated urodynamic tests, such as cystometry, voiding cystometry, video-urodynamics are recommended for patients with multi-symptomatic forms of bladder dysfunctions.

First urodynamic tests in children after spina bifida surgery with suspected NBD should be performed as early as in infancy; the subsequent tests ought to be the control ones[10].

An infant with suspected NBD post spinal cord surgery should first undergo physical examination, with particular attention paid to the condition of the genitourinary system. Physical appearance, sensation and neurological reflexes in the perineal region should be evaluated. Special attention should be paid to the manner of urinating; spontaneous urine discharge from the urethra in droplets is often detected, sometimes urine leakage after the pressing above the pubic symphysis is observed.

The tonus of anal sphincters should be checked, which is predominantly found to be totally lacking. When introducing a catheter into the bladder, the examining physician observes the child's reactions, which enables evaluation of the urethra sensation.

From among many parameters evaluated in the urodynamic test, the ones considered most significant for the prognostic evaluation of the risk of complications occurrence are the 'Leak point volume' (LPV) and the 'Leak point pressure' (LPP), i.e. the capacity and pressure at which the urine from the filled bladder starts to leak. The increased risk of development of complications occurs in patients with LPP > 40 cm H_2O[3,10-12].

The treatment of patients with neurogenic dysfunctions of the urinary system is a multi-directional and complicated process. Generally it may be divided into treatment of causes and treatment of complications.

The treatment of causes, i.e. the correction of pathology in the function of the LUT, is considered fundamental. That treatment begins with the conservative methods. The two most important forms of treatment of severe NBD are clean intermittent catheterization and pharmacological treatment of functional disorders found in urodynamic studies[4,13-16].

Early institution of conservative treatment in children diagnosed with the NBD is essential, as serious complications in the urinary tract develop in more than 40% of untreated patients after spina bifida operations[17].

Long-term prophylactic therapy of urinary tract infections has a debatable value in the protection against the development of complications in the urinary system.

A child with a severe form of NBD (which is the form encountered in a majority of children with open meningomyelocele), having no urethral sensation and no feeling of bladder fullness, cannot urinate in a controlled manner. In such children, urine leakage occur whenever the intravesical pressure is higher than the pressure generated by sphincters. Therefore, condition that is particularly dangerous for such patients is overactivity of urethral sphincters, detrusor-sphincters dyssynergy (DSD) i.e. absence of relaxation reaction of the sphincters during urination.

Thus, the main goal in the treatment of the NBD is first of all improvement of the urine voiding phase, i.e. enabling the efficient periodic evacuation of urine from the bladder. This is provided predominantly through CIC, which may also be supported with pharmacological treatment. In order to improve miction, selective alpha-blockers, myorelaxans are used. The effectiveness of pharmacological treatment has not been clearly confirmed and, therefore, the CIC should be considered the safest[3,13,18-20].

Literature on the subject brings more and more reports on the effectiveness of procedures that consist in injecting Botulinum-A toxin preparations into the bladder walls or sphincters in patients with NBD. Such procedures result in increased bladder capacity with decrease in intravesical pressure or lowered pressures at the leakage of urine from the bladder with the accompanying decrease of the volume of residual urine[21-24].

Other non-pharmacological methods of treatment of pathology in the voiding phase (biofeedback, electrostimulation, electromodulation) have a limited use in children with neurogenic bladder and may only be employed for patients with less severe damages to the nervous system and with preserved sensation in the organs of the LUT[3,25-27].

In the storage phase, the most vital problem is the detrusor overactivity (DO), that is overcontractility of the bladder muscle uncontrolled by the central nervous system. Those contractions lead to the increase of intravesical pressure in the storage phase and, together with lowered compliance of the bladder walls, are responsible for decreased functional bladder capacity.

From the practical point of view, in children with NBD we evaluate the maximal anatomic bladder capacity (Vol_{max}) that is reflected by maximal volumes of catheterized urine and average functional bladder capacity (Vol_{av}) i.e. the volume at which normally urine leakage occurres.

A phenomenon characteristic for children with NBD and DO is that from time to time parents obtain large amounts of catheterized urine, corresponding to EBC, while during the day amounts of catheterized urine are various, often small, leading to urine leakage relatively shortly after catheterization. This leads to increased urinary incontinence[3].

Other pathology more rarely found in urodynamic tests in children with spina bifida and requiring treatment are detrusor areflexia and sphincter hypofunction. Sphincter incompetence is mainly responsible for urine incontinence.

Types of Complications of the Bladder Dysfunctions – Our Own practical Classification

We propose the following classification of complications characteristic for the bladder and sphincter dysfunctions: (1) Urinary tract infections; (2) Urolithiasis; (3) Anatomic changes in the lower urinary tract; (4) Anatomic changes in the upper urinary tract; (5) Functional disturbances of kidneys parenchyma; (6) Urinary incontinence.

Urinary tract infections (UTI)

The UTI are caused both by pathology in the voiding phase, leading to residual urine after miction, and the pathology in the storage phase leading to the increase of pressure in the bladder above the values considered as safe.

High pressure in the bladder in both the storage phase and the voiding phase results in infections of the urinary tract, as it leads to decreased blood perfusion in the vessels of the bladder wall. The ischaemia, in turn, leads to damage of the urothelium. The ischaemic urothelium becomes ineffective in its role of protecting the bladder against the invasion of bacteria.

The consequences of UTI are: prolonged treatment with antibiotics and the resulting imbalances in the patient's bacterial flora, viral and mycotic superinfections, as well as secondary immunity disorders. Recurrent, chronic infections also have an impact on the development and progressing anatomic changes in both upper and LUT. The most often found ones include thickening of bladder walls, upper urinary tract dilatation and post-inflammatory scarring of the renal parenchyma.

Symptomatic UTI must be differentiated from asymptomatic changes in urinalysis in the form of leucocyturia often encountered in catheterized children. It is believed that such symptomless changes in urinanalysis, do not require therapy with antibiotics.

Performing routine urine culture in children presenting no symptoms of active infection should be considered pointless. Microbiological tests are of fundamental importance for hospitalized children in which we suspect infection with hospital bacterial strains that are characterized by high resistance to antibiotics.

In patients with NBD we may encounter various forms of symptomatic infections of the urinary tract. The infection may be limited to the bladder; it may be acute, but it often turns into the chronic form. The specific varieties of the chronic infection of the bladder are cystitis cystica or cystitis interstitialis. The infection may progress to the upper urinary tract resulting in a fully-developed *pyelonephritis*. If there is a coexistance of hydronephrosis, pyonephrosis may develop, with septic course more frequently occurring in younger children[17,28-31].

Urolithasis

Calculus deposits are found in the renal collection systems, in the ureters and in the bladder.

There are numerous factors that influence the forming of stones, such as UTI, urinary retention caused by anatomic changes in the urinary tract (hydronephrosis, obstructive megaureter, vesicoureteral reflux, bladder diverticula) or residuals resulting from ineffective miction.

Other factors leading to urolithiasis include decreased physical activity, remaining in one position and limited fluid intake.

Treatment of urolithiasis, particularly staghorn calculi, in patients with NBD is a considerable clinical problem. The choice of the treatment method depends on the location and size of the stone, its shape, as well as technical capabilities

of the medical centre. In paediatric urology, minimally invasive techniques such as ESWL or PCNL become increasingly important. However, some cases still require operative treatment[32-37].

Anatomic Changes in the LUT Tract Are he Consequence of High Pressures in the Storage Phase and the Presence of Subvesical Obstruction Combined with a Chronic UTI

Bladder dysfunctions also lead to changes in the histopathological structure of the bladder wall manifesting themselves mainly by the atrophy of muscle fibres together with progressing fibrosis and the muscle tissue being replaced by the connective tissue.

Imaging studies reveal hypertrophy of the bladder wall often coexisting with diverticula.

In cystoscopy, the bladder wall show trabeculation; numerous diverticula of the bladder wall are visible and in cases of the co-existing vesico ureteric reflux, pathologies of the ureter orifices are detected[4,17,38].

Anatomic Changes in the Upper Urinary Tract

Vesicoureteral reflux (VUR) is one of the consequences encountered in patients with detrusor-sphincter dysfunctions.

The classic five-degree grading is used to describe the severity of VUR. However, in the light of the recent knowledge about the bladder function, that division seems insufficient for the planning of VUR treatment in children with bladder dysfunctions.

The classic VUR grading seems to be unsatisfactory, as it fails to take into account the influence of functional parameters on the image of the bladder and ureters as seen on the monitor during video-urodynamic studies.

The analysis of the results of video-urodynamic studies indicates the predominant impact of bladder dysfunctions on the origination of VUR and on the appearance of the ureters into which the urine flows. During video-urodynamic or fluoroscopic testing, transitory refluxes occurring only during overactive bladder contractions are observed in some patients. Another interesting phenomenon is urine reflux from the bladder to the dilated renal pelvis through the narrow ureter.

VUR may lead to considerable widening of the ureters – the so-called 'refluxing megaureter', yet in some patients urinary retention in dilated ureters persists after bladder emptying with a catheter testifying to the existence of an obstruction of the ureteral orifice in the bladder wall, the so-called 'refluxing stenotic megaureter'.

Apart from the above-listed shortcomings, the classic five-degree grading fails to take into consideration the key parameter which is the intravesical pressure at which urine begins to flow from the bladder into the ureter. That parameter is possible to be determined only in video-urodynamic study and affects the decision concerning the choice of the treatment method.

In cases of reflux caused by high intravesical pressures we recommend treatment of the reflux cause, i.e. decreasing of pressures in the bladder pharmacologically or operatively without the necessity to perform the anti-reflux surgery.

Occurrence of the reflux with low pressures is a proof of a damage to the anti-reflux mechanism in the bladder wall and indicates the necessity of endoscopic treatment or even anti-reflux operation of the ureter[39-43].

Associating hydronephrosis, a pathology essentially consisting in the obstruction at the pyelo-ureteric junction, with the NBD remains disputable, yet in some children with neurogenic bladder the dilation of the renal pelvis without ureter dilatation is observed.

The end stage form of renal damage caused by improperly functioning LUT is renal atrophy with renal failure. A small, non-functioning kidney may require nephrectomy due to hypertension or when this kidney is a source of infections, often caused by co-occurring urolithiasis[28,29,38,44].

Functional Changes in the Kidney

Data about the impairment of the nephron function in the situation of persisting high pressures in the bladder are scarce. Still, functional tests of the renal parenchyma do reveal impairment of the secretory function of the kidneys in cases of high-pressure dysfunctions of the bladder. High intravesical pressure is transmitted to the upper urinary tract (kidney barotrauma) causing decreased blood circulation to the kidney, decreased glomerular filtration and deterioration of urine flow from the renal collection system to the bladder. Barotrauma may lead to progressing renal failure[4,17,29,38,45,46].

Urinary Incontinence

Regardless of the pathology found in urodynamic tests, the most frequent complication of detrusor-sphincter dysfunctions is urinary incontinence.

Urinary incontinence is uncontrolled leakage of urine from the bladder in the storage phase or loss of the ability to consciously postpone from urination and to choose the time and place for urination.

According to the definition proposed by the WHO: health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Urinary incontinence may be considered an illness in all these three categories.

Treatment of urinary incontinence in patients with NBD requires a thorough analysis of particular urodynamic tests, beginning from the Voiding Diary through uroflowmetry with ultrasound residual estimation to video-urodynamic studies.

Urinary incontinence may be treated with both pharmacotherapy and non-pharmacological rehabilitation techniques of the LUT. Surgical interventions may also be suggested to patients, yet are treated as a last resort.

Anticholinergics are the first choice in the pharmacological treatment of children with incontinence caused by bladder dysfunction. None of those drugs is authorized for use in infants and small children; only oxybutynin holds a formal authorization, but for children above 5 years of age. Solifenacin (Vesicare), mirabegron (Betmiga), tolterodine (Uroflow), fesoterodine (Toviaz) trospium chloride (Sanctura) and propiveryne (Mictonorm) are drugs with an easier dosing regime, once or twice daily. In comparative studies with oxybutynin carried out on adults, side effects of those drugs were found to be less frequent and less intense[3,4,15,16].

According to the 7th report of the ICS Standardization Committee, non-pharmacological rehabilitation techniques are: Kegel exercises, biofeedback techniques, change of incorrect habits related to urination, electrostimulation and electromodulation, as well as catheterization[13,25,26,47].

There are many techniques used in the operative treatment of patients with NBD that improve both the functions of the urinary tract and quality of life. Operative procedures may enlarge the native bladder or replace the bladder with an intestinal pouch.

Operative treatment is suggested to patients who have been treated conservatively with no satisfactory bladder capacity obtained or who have developed complications; those operative procedures include augmentation and autoaugmentation operations. For bladder augmentation the small intestine, colonic segments, stomach, or the dilated ureter of the non-functioning kidney may be used. Augmentation operatios are undertaken with the goal of increasing the functional capacity of the bladder, decreasing intravesical pressure through the liquidation of overactive detrusor overactitvity and increasing the compliance of the bladder walls[39-43,48,49].

However, those surgical interventions carry the risk of perioperative and postoperative complications[50-52].

In recent years, more reports have appeared in literature on the results of using Botulinum-A toxin preparations in the treatment of patients, both adults and children, with NBD. The endoscopic administration of the Botulinum-A toxin into the detrusor causes temporary paralysis of muscle fibres, and consequently decreases the pressure in the storage phase and increases the functional capacity of the bladder. Positive effects of intravesical administration of Botulinum-A toxin on both bladder function and the urinary tract morphology have been demonstrated[4,21,22,24,53].

In many patients who have undergone bladder augmentation, a continent stoma is formed at the same time in order to empty the bladder. Such a stoma is most often made from the appendix (a Mitrofanoff stoma), and in the absence of the appendix it may be made from the small intestine (a Monti procedure)[54,55].

An issue still under discussion is the necessity of neoimplantation of ureters in children with vesicoureteral reflux who undergo bladder augmentation[39-43].

Other types of operative procedures are various urine diversions, i.e. incontinent stomas. Vesicocutaneous stomas offer a solution of relative technical simplicity and are well accepted by parents of infants, mainly those with bilateral changes in the upper urinary tract.

When changes relate to one ureter or kidney, one may consider renal loop ureterocutaneostomy. Due to frequent complications and difficulties during reconstructive surgeries, the performance of terminal ureterocutaneostomies is not currently recommended[49,56,57].

In children with the NBD, in rare cases operations are performed because of sphincter incompetence. Such surgery may be justified only in rare cases of children with the Leak Point Pressure below 20 cm H_2O. For such operations, sling techniques known from female stress incontinence operations and even operations of artificial sphincter implantation are used[58,59].

Conclusions

Proposed practical classification of complications of bladder and sphincter dysfunctions is clear and simple. This classification could be used both in children with neurogenic and non-neurogenic LUTD. It is helpful in planning follow-up procedures and evaluation of treatment results.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Stöhrer M, Goepel M, Kondo A, Kramer G, Madersbacher H, Millard R, Rossier A, Wyndaele JJ. The standardization of terminology in neurogenic lower urinary tract dysfunction with suggestions for diagnostic procedures. Neurourol Urodyn 1999; 18: 139-158.
2) Ahlberg J, Edlund C, Wikkelsö C, Rosengren L, Fall M. Neurological signs are common in patients with urodynamically verified "idiopathic" bladder overactivity. Neurourol Urodyn 2002; 21: 65-70.
3) Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol 2015; 14: 720-732.
4) Verpoorten C, Buyse GM: The neurogenic bladder: medical treatment. Pediatr Nephrol 2008; 23: 717-725.
5) Watanabe T, Vaccaro AR, Kumon H, Welch WC, Rivas DA, Chancellor MB. High incidence of occult neurogenic bladder dysfunction in neurologically intact patients with thoracolumbar spinal injuries. J Urol 1998; 159: 965-968.
6) Satar N, Bauer SB, Shefner J, Kelly MD, Darbey MM. The effects of delayed diagnosis and treatment in patients with an occult spinal dysraphism. J Urol 1995; 154: 754-758.
7) Hjälmås K. Urodynamics in normal infants and children. Scand J Urol Nephrol Suppl 1988; 114: 20-27.
8) Neveus T, von Gontard A, Hoebeke P, Hjalmas K, Bauer S, Bower W, Jørgensen TM, Rittig S, Walle JV, Yeung CK, Djurhuus JC. The standardisation of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006; 176: 314-324.
9) Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci 2008; 9: 453-466.
10) Kessler TM, Lackner J, Kiss G, Rehder P, Madersbacher H. Predictive value of initial urodynamic pattern on urinary continence in patients with myelomeningocele. Neurourol Urodyn 2006; 25: 361-367.
11) McGuire EJ, Woodside JR, Bordin TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981; 136: 205-209.
12) Bauer SB, Hallet M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, Colodny AH, Retik AB. Predective value of urodynamic evaluation in newborns with myelodysplasia. JAMA 1984; 252: 650-652.
13) Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean intermittent self-catheterization in the treatment of urinary tract disease. J Urol 1972; 107: 458-61.
14) Wyndeale JJ, Maes D. Clean intermittant self-catheterisation: a 12-year followup. J Urol 1990; 143: 906-908.
15) Edelstein RA, Bauer SB, Kelly MD, Darbey MM, Peters CA, Atala A, Mandell J, Colodny AH, Retik AB. The long-term urological response of neonates with myelodysplasia treated proactively with intermittent catheterization and anticholinergic therapy. J Urol 1995; 154: 1500-1504.
16) Andersson KE, Chapple CR. Oxybutynin and the overactive bladder. World J Urol 2001; 19: 319-323.
17) Smith ED. Urinary prognosis in spina bifida. J Urol 1972; 108: 815-817.
18) Abrams P, Amarenco G, Bakke A, Buczy ski A, Castro-Diaz D, Harrison S, Kramer G, Marsik R, Prajsner A, Stöhrer M, Van Kerrebroeck P, Wyndaele JJ. European Tamsulosin Neurogenic Lower Urinary Tract Dysfunction Study Group. Tamsulosin: efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. J Urol 2003; 170: 1242-1251.
19) Austin PF, Hossy YL, Masel JL, Cain MP, Casale AJ, Rink RC. Alpha-adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction. J Urol 1999; 162: 1064-1067.
20) Bogaert G, Beckers G, Lombaerts R. The use and rationale of selective alpha blockade in children with non-neurogenic neurogenic bladder dysfunction. Int Braz J Urol 2004; 30: 128-134.
21) Marte A, Vessella A, Cautiero P, Romano M, Borrelli M, Noviello C, Del Gado R, Parmeggiani P. Efficacy of botulinum toxin-A for treating intractable bladder hyperactiviy in children affected by neuropathic bladder secondary to myelomeningocele: an alternative to enterocystoplasty. Minerva Pediatr 2005; 57: 35-40.
22) Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005; 174: 984-989.
23) Leippold T, Reitz A, Schurch B. Botulinum toxin as a new therapy option for voding disorders: current state of the art. Eur Urol 2003; 44: 165-174.

24) Altaweel W, Jednack R, Bilodeau C, Corcos J. Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. J Urol 2006; 175: 1102-1105.

25) Wheeler JS, Walter JS, Zaszczurynski PJ. Bladder inhibition by penile nerve stimulation in spinal cord injury patients. J Urol 1992; 147: 100-103.

26) Madersbacher H. Intravesical electrical stimulation for the rehabilitation of the neuropathic bladder. Paraplegia 1990; 28: 349-352.

27. Maternik M, Krzeminska K, Zurowska A. The management of childhood urinary incontinence. Ped Nephrol 2015; 30: 41-50.

28. Cameron AP, Rodriguez GM, Schomer KG. Systematic review of urological followup after sipnal cord injury. J Urol 2012; 187: 391-397.

29) Whiteneck GG, Charlifue SW, Frankel HL, Fraser MH, Gardner BP, Gerhart KA, Krishnan KR, Menter RR, Nuseibeh I, Short DJ, Silver JR. Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. Paraplegia 1992; 30: 617-630.

30) Matsumo T, Takanashi K, Manabe N, Iwatsubo E, Mawakami Y. Urinary tract infection in neurogenic bladder. Int J Antimicrob Agents 2001; 17: 293-297.

31) Gamé X, Castel-Lacanal E, Bentaleb Y, Thiry-Escudié I, De Boissezon X, Malavaud B, Marque P, Rischmann P. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol 2008; 53: 613-618.

32) Hillman LJ, Burns SP, Kraft GH. Neurological worsening due to infection from renal stones in a multiple sclerosis patient. Mult Scler 2000; 6: 403-406.

33) Takasaki E, Suzuki T, Honda M, Imai T, Maeda S, Hosoya Y. Chemical composition of 300 lower urinary tract calculi and associated disorders in the urinary tract. Urol Int 1995; 54: 89-94.

34) Vaidyanathan S, Krishnan KR, Soni BM, Fraser MH. Unusual complications of intermittant self-catheterisation in spinal cord injury patients. Spinal Cord 1996; 34: 745-747.

35) Vespasini G, Pesce F, Finazzi AE, Virgili G, Giannatoni A, Micali S, Micali F. Endoscopic ballistic lithotrypsy in the treatment of bladder calculi in patients with neurogenic voiding dysfunction. J Endourol 1996; 10: 551-554.

36) Ozokutan BH, Kucukaydin M, Gunduz Z, Kabakli-oglu M, Okur H, Turan C. Urolithiasis in childhood. Ped Surg Int 2000; 16: 60-63.

37) Jayanthi VR, Arnold PM, Koff SA. Strategies for managing upper tract calculi in young children. J Urol 1999; 162: 1234-1237.

38) Seki N, Akazawa K, Senoh K, Kubo S, Tsunoda T, Kimoto Y, Naito S. An analysis of risk faktors for upper urinary tract deterioration in patients with myelodysplasia. Br J Urol 1999; 84: 679-682.

39) Simforoosh N, Tabibi A, Basiri A, Noorbala MH, Danesh AD, Ijadi A. Is ureteral reimplantation necessary during augmentation cystoplasty in patients with neurogenic bladder and vesicoureteral reflux? J Urol 2002; 168: 1439-1441.

40) Nasrallah PF, Aliabadi HA. Bladder augmentation in patients with neurogenic bladder and vesicoureteral reflux. J Urol 1991; 146: 563-566.

41) Hayashi Y, Kato Y, Okazaki T, Lane GJ, Kobayashi H,Yamataka A. The effectiveness of ureteric reimplantation during bladder augmentation for high-grade vesicoureteric reflux in patients with neurogenic bladder: long-term outcome. J Pediatr Surg 2007; 42: 1998-2001.

42) Helmy TE, Hafez AT. Vesicoureteral reflux with neuropathic bladder: studying the resolution rate after ileocystoplasty. Urology 2013; 82: 425-428.

43) López Pereira P, Martinez Urrutia MJ, Lobato Romera R, Jaureguizar E. Should we treat vesicoureteral reflux in patients who simultaneously undergo bladder augmentation for neuropathic bladder? J Urol 2001; 165: 2259-2261.

44) McLorie GA, Perez-Marero R, Csima A, Churchill BM. Determinants of hydronephrosis and renal injury in patients with myelomeningocele. J Urol 1988; 140: 1289-1292.

45) Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology 2001; 20: 138-143.

46) Kaneti J, Sober I, Gradus D. Fate of nonneurogenic neurogenic bladder – end stage renal failure. Eur Urol 1988; 14: 422-425.

47) Singh G, Thomas DG. Intermittent catheterization following enterocystoplasty. Br J Urol 1995, 76: 175-178.

48) Di Benedetto V, Monfort G. Stomach versus sigmoid colon in children undergoing major reconstruction of the lower urinary tract. Pediatr Surg Int 1997; 12: 393-396.

49) Hendren WH. Some alternatives to urinary diversion in children. J Urol 1978; 119: 652-660.

50) Braverman RM, Lebowitz RL. Perforation of the augmented urinary bladder in nine children and adolescents: importance of cystography. Am J Roentgenol 1991; 157: 1059-1063.

51) Hendren WH, Hendren RB. Bladder augmentation: experience with 129 children and young adults. J Urol 1990; 144: 445-453.

52) González R, Ludwikowski BM. Alternatives to conventional enterocystoplasty in children: a critical review of urodynamic outcomes. Front Pediatr 2013; 1: 1-9.

53) Schulte-Baukloh H, Michael T, Sturzebecher B, Knispel HH. Botulinum-A toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. Eur Urol 2003; 44: 139-143.

54) Suzer O, Vates TS, Freedman AL, Smith CA, Gonzalez R. Results of the Mitrofanoff procedure in urinary tract reconstruction in children. Br J Urol 1997; 79: 279-282.

55) Gerharz EW, Tassadaq T, Pickard RS, Shah PJ, Woodhouse CR, Ransley PG. Transverse retubularized ileum: early clinical experience with a new second line Mitrofanoff tube. J Urol 1998; 159: 525-528.

56) Stein R, Fisch M, Stockle M, Demirkesen O, Hohenfellner R. Colonic conduit in children: protection of the upper urinary tract 16 years later? J Urol 1996; 156: 1146-1150.

57) Nomura S, Ishido T, Tenanishi J, Makiyama K. Long-term analysis of suprapubic cystostomy drainage in patients with neurogenic bladder. Urol Int 2000; 65: 185-189.

58) Nurse DE, Mundy AR. One hundred artificial sphincters. Br J Urol 1988; 61: 318-325.

59) Simeoni J, Guys JM, Mollard P, Buzelin JM, Moscovici J, Bondonny JM, Melin Y, Lortat-Jacob S, Aubert D, Costa F, Galifer B, Debeugny P. Artificial urinary sphincter implantation for neurogenic bladder: a multi-institutional study in 107 children. Br J Urol 1996; 78: 287-293.