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Upper urinary tract deterioration and possible etiologies in intractable voiding dysfunction: Role of occult spinal malformation

Dirençli işeme fonksiyon bozukluğu olan çocuklarda üst üriner sistem hasarı ve gizli spinal disrafizmin etkisi

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ABSTRACT

Objectives: To evaluate the presence of upper urinary tract deterioration (UUTD) and accompanying pathologies in children treated with the diagnosis of non-neurogenic bladder-sphincter dysfunction (NNBSD).

Patients and Methods: We retrospectively reviewed the medical records of 316 consecutive patients with NNBSD who were treated. All cohort were grouped into two: Group I (Treatment success; n=284), Group II (Treatment failure with any form of occult spinal pathology; n=32). Thirty-four children with treatment-failure and normal magnetic resonance imaging (MRI) findings were excluded. Groups were compared for pre- and post-treatment pediatric lower urinary tract symptom score (PLUTSS), presence of UUTD and urodynamic findings.

Results: The mean PLUTSS was significantly less in Group I compared with Group II at pre-treatment and 3 months thereafter the initial treatment (12.20 ± 5.90 and 5.20 ± 4.90 vs 20.3 ± 2.14 and 18 ± 3.4, respectively $p<0.01$). The mean cystometric capacities and detrusor leak point pressure (DLPP) of Group II prior to initial treatment and after 6 months of the untethering surgery were found to be 194, 267 mL and 28, 12cm H2O, respectively ($p<0.05$). Presence of UUTD was significantly correlated with DLPP >20 cm H2O and presence of vesicoureteral reflux (VUR).

Conclusion: UUTD in NNBSD is more common in children with occult spinal pathology, than in those without.

Keywords: Non-neuropathic bladder sphincter dysfunction, Upper urinary tract deterioration, Symptom score

ÖZ

Amaç: Nörojenik olmayan mesane–sfinkter fonksiyon bozukluğu (NOMSFB) tanısıyla tedavi edilen çocuklarda üst üriner sistem hasarı (ÜÜSH) ve eşlik eden patolojilerin araştırılmasıdır.

Hastalar ve Yöntemler: NOMSFB nedeniyle kliniğimizde tedavi edilen 316 çocuğun tıbbi kayıtları retrospektif olarak incelendi. Çocuklar, tedavi yanıtına ve magnetic resonans görüntüleme (MRG) bulgularına göre iki gruba ayrıldılar: Grup I (Tedaviye yanıt verenler; n=284) ile Grup II (Tedaviye dirençli olup, lomber MRG'sinde gizli spinal disrafizm bulgusu olanlar; n=32). Tedaviye dirençli olup lomber MRG'sinde patoloji saptanmayan 34 çocuk çalışma dışı bırakıldı. Gruplar tedavi öncesi ve sonrası semptom skoru (SS), ÜÜSH ile ürodinami bulguları açısından karşılaştırıldı.

Bulgular: Tedavi öncesi dönemde ve tedavi başladıktan üç ay sonra, Grup I'in ortalama SS'si Grup II'ye göre anlamlı olarak düşük saptandı (sırasıyla 12,20 ± 5,90 ve 5,20 ± 4,90 karşın 20,3 ± 2,14 ve 18 ± 3,4; $p<0.01$). Grup II'nin başlangıç tedavisi öncesi ortalama sistometrik kapasitesi ve detrüsör kaçırma anı basıncı (DKAB) sırasıyla 194 ml ve 28 cm H2O olarak saptandı. Grup II'nin gergin omurilik onarımını takip eden altıncı ayda ortalama sistometrik kapasite ve ortalama DKAB sırasıyla 267 ml ve 12 cmH2O olarak saptandı. ÜÜSH varlığı ile DKAB'ın 20 cmH2O üzeri olması ve vezikoüreteral reflü varlığı arasında anlamlı ilişki bulundu.

Sonuç: NOMSFB'da ÜÜSH, gizli spinal disrafizm varlığında daha sık görülür.

Anahtar kelimeler: Nörojenik olmayan mesane-sfinkter fonksiyon bozukluğu, Üst üriner sistem hasarı, Semptom skoru

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Introduction

Non-neurogenic bladder-sphincter dysfunction (NNBSD) is a frequently seen pathology in daily clinical practice of pediatric urology. Functional urinary incontinence and upper urinary tract deterioration (UUTD) are the most important complications of untreated NNBSD [1-4]. There seems to be a strong association between NNBSD and recurrent urinary tract infection (UTI) with or without accompanying vesicoureteral reflux (VUR) [2-4]. Treatment of NNBSD is essential in the management of recurrent UTI and VUR, as this prevents kidney damage [5, 6].

Dysfunctional voiding (DV), overactive bladder (OAB), and underactive bladder (UAB) are the main clinical outcomes of NNBSD [3]. Children with NNBSD who fail to respond to initial treatment should undergo a series of clinical study including urodynamics and lumbosacral magnetic resonance imaging (MRI) for the assessment of any occult spinal pathology [6, 7]. Afshar et al., reported that in a population of 73 NNBSD patients, 3 of 35 (8.6%) that failed in medical management had occult pathology [8]. Spinal dysraphism occurs in two forms: an open form named spina bifida aperta, and a closed form named spina bifida occulta. Either form of spinal deformity may feature as a progressive form of neurological deterioration called tethered cord syndrome which will finally need a neurosurgical intervention. MRI can be used to differentiate such neurologic abnormalities in patients with spinal dysraphism [9].

Generally UUTD with lower urinary tract dysfunction (LUTD) is related to tethered cord, thus one can expect similar predisposing factors for UUTD like in NNBSD [7]. Such factors include UTI, ongoing VUR, a high bladder filling and/or voiding pressure, and discoordinated voiding.

The aim of the current study was to evaluate the presence of UUTD and the related conditions in patients who have received an optimal treatment for NNBSD and yet were identified as having occult spinal pathology, both during treatment and during the early follow up period.

Patients and Method

Study Population

The study involved children who were diagnosed with NNBSD after admission to Marmara University, School of Medicine, Pediatric Urology Outpatient Clinic between November 2010 and June 2015. All cohort had one or more of the following symptoms: daytime and/or nighttime urinary incontinence, holding maneuvers, perceived incomplete emptying, urinary urgency, post-micturition dribble, weak stream, urinary hesitancy, intermittency, increased urinary frequency and UTI. Medical records of each patient were retrospectively reviewed. Categories of patients with NNBSD were identified (methods detailed below) and respective management protocols were applied. Children who responded to treatment for NNBSD were grouped as Group I. Those who did not respond to treatment underwent further testing, and study group was established based on these findings.

Initial Diagnostics

Pediatric Lower Urinary Tract Symptom Score (PLUTSS): This score was originally developed and validated by Akbal et al. [10] (Fig. 1). This instrument has been widely used for clinical assessment of LUTD and has also been applied in research studies [11, 12]. Similar tools have also been reported to be used to assess children with lower urinary tract symptoms [13]. The PLUTSS was administered to each child and to his/her parents at initial clinical evaluation period (pre-treatment) and repeated in every 6 months periods thereafter (post-treatment). For each patient, the pre-treatment PLUTSS and the 6 months of post-treatment PLUTSS were used for the study.

Other Tests: Each patient underwent a combined uroflowmetry assessment with electromyography (EMG). Total bladder capacity was calculated by adding voided urine volume to measured post-voiding residual urine volume under ultrasonography (USG), and was expressed as a percentage of age-expected bladder capacity [14]. Each patient also completed a bladder diary for two days with the recommended entries of ICCS [14]. For the assessment of possible UUTD (i.e., hydronephrosis, parenchymal thinning, atrophy) each child underwent a routine imaging with USG. Those confirmed to have UTI and abnormal USG findings were further evaluated with voiding cystourethrography (VCUG). Grading of VUR was done according to the international classification [15, 16]. Children with VUR underwent a dimercaptosuccinic acid (DMSA) scan and the results of the scan were summarized as either normal or scarring for the present study [17].

Disease Categories and Management

Based on initial diagnostics, patients with NNBSD were categorized as OAB, DV, or UAB. Patients with OAB were treated with timed voiding regimens, medications of anticholinergics and/or antibiotics. Anticholinergic treatment

was done with oxybutynin in a dosage of 0.2 mg/kg via the enteral route. Patients with only nocturnal enuresis were advised to limit fluid intake in the evening and to urinate before going to bed. Those resistant to initial treatment for nocturnal symptoms were prescribed oral desmopressin (DDAVP) or alarm therapy, as recommended in pediatric urology guidelines [18].

Dysfunctional voiding was treated with timed voiding and positive reinforcement regimens, bowel regimens (including high daily fluid intake, a diet high in fiber, and stool softeners if necessary), biofeedback therapy, medications of alpha-blockers and/or antibiotics [19].

Underactive bladder was treated with clean intermittent catheterization and antibiotic prophylaxis. Bowel regimens were prescribed for patients with UAB who also had bowel problems.

Additional Diagnostic Testing in Cases of No Response

Children were treated for a minimum of 3 months before they were identified as non-responders. Based on pre- versus post-treatment PLUTSS results and discussion with patients and parents, "No response to treatment" was defined as any reduction of symptoms below 49% [14]. All of these children named as non-responders underwent urodynamic and radiographic assessments.

Urodynamic Evaluation: Standard filling cystometry (AYMED, Locum Wireless Urodynamic System, Turkey) was performed with the patient in supine position, using a 6F double-lumen urethral cystometry catheter and filling rate was taken as 5% to 10% of predicted bladder capacity ((age+1)x30) per minute [14]. According to a report from the Standardization Committee of the International Continence Society [20] and International Children's Continence Society [21], we calculated the maximum detrusor pressure (P detmax, cm H_2O), maximum cystometric capacity (MCC, ml), DLPP (cmH_2O). Namely, The International Continence Society (ICS) defines the DLPP as the value of the lowest detrusor pressure at which leakage occurs in the absence of abdominal pressure rise. The DLPP was measured by marking the lowest pressure at the moment when the urine seeped out from the urethral meatus.

RadiographicEvaluation: A spinal MRI was performed and any finding of conus medullaris below the lower endplate of the L2 vertebra, lipoma or thickening of the filum terminale, and/or vertebral anomalies was considered as abnormal [9].

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v. 20, IBM Corporation, NY, USA). Findings for pre-treatment and six-months-post-treatment SS were compared using the unpaired Student's t test. Relationships between presence of UUTD and urodynamic parameters were assessed using Pearson correlation analysis. P values <0.05 were considered significant.

Results

Of all 388 children a total of 34 children with NNBSD resistant to pharmacotherapy-urotherapy were excluded from the study, as they were candidates for other invasive treatment modalities (i.e., neuromodulation strategies, intradetrusor botulinium toxin A injection, or augmentation cystoplasty). Thirty-eight patients were lost to follow up. Group I patients (n=284) consisted of NNBSD and treated with standard modalities and follow-up. Group II patients (n=32) were children with NNBSD resistant to pharmacotherapy-urotherapy and were diagnosed as having any form of occult spinal pathology in further evaluation.

The mean follow-up time of the patients in the present study was 13.6 ± 7.8 months (range, 6-26 months). The mean ages of Groups I and II were not significantly different (8 ± 2.1 vs. 7 ± 2.3 years, respectively; p>0.05).

Of all the children in Group I, 97 had DV (34%), 170 had OAB (60%) and 17 had UAB (6%). The mean PLUTSS results of the Group I patients at the pre-treatment period and 3 months thereafter was found to be 12.2 ± 5.9 and 5.2 ± 4.9, respectively.

Of all the children in Group II, 19 had DV (59%) and 13 had OAB (41%). The mean PLUTSS results of the Group II patients at the pre-treatment period and 3 months thereafter was found to be 20.3 ± 2.1 and 18 ± 3.4, respectively. The mean PLUTSS at the first 6th month period following untethering surgery was found to be 12.2 ± 1.8. This final score was found to be significantly lower than the pre-treatment PLUTSS (p<0.001), indicating an appropriate treatment for NNBSD.

Additional Testing - Urodynamic Findings

The mean cystometric capacities and mean DLPP of Group II prior to initial treatment was found to be 194 mL (min 45 mL, max 302 mL) and 28 cm H_2O (min 4 cm H_2O, max 58 cm H_2O), respectively. The mean cystometric capacities and the mean DLPP of Group II patients after 6 months of

the untethering surgery was found to be 267 mL (min 145 mL, max 335 mL) and 12 cm H2O (min 4 cm H2O, max 20 cm H2O), respectively ($p<0.05$).

Upper Urinary Tract Deterioration

In the initial evaluation period of Group II, of all patients, 12 (37.5%) were found to have an UUTD on DMSA scanning. During the follow-up period 10 (83.3%) of these 12 patients who had initial renal scars were seemed to be stabilized.

At initial assessment in Group II patients, 4 had VUR and 8 had a DLPP >20 cm H_2O. Presence of an UUTD was significantly correlated with two occasions; either having a DLPP>20 cm H_2O or having an accompanying VUR (Table II).

The proportion of patients with a history of recurrent UTI in Group II was significantly higher than that in Group I (76.5% vs. 31.2%, respectively; $p<0.001$) (data not shown).

Table I: The initial relation of upper urinary tract deterioration (UUTD) and detrusor leak point pressure (DLPP) in Group II patients prior to treatment is shown

	UUTD Absent (n)	UUTD Present (n)	Total (n)
DLPP > 20 cm H_2O	8	8	16
DLPP < 20 cm H_2O	14	2	16
Total	22	10	32

Table II: The significance of having a correlation with an upper urinary tract deterioration prior to treatment is given for some instances like a detrusor leak point pressure (DLPP) >20 cm H_2O, presence of vesicoureteral reflux (VUR), and recurrent urinary tract infection (UTI). (r value of Pearson Correlation is given with its statistical significance)

	r value	p value
DLPP >20 cm H_2O	0.459	<0.001
VUR	0.322	<0.01
Recurrent UTI	0.161	>0.05

Discussion

The findings of the present study, suggested a higher incidence of UUTD for patients with functional urinary incontinence that do not respond to treatment, if they had any occult spinal pathology. Of all the patients with functional urinary incontinence (n=388) only 8.8% (n=34) did not respond to our initial treatment regimen, and of these patients with treatment failure, almost all (n=32) were diagnosed as having tethered cord malformation. Considering the previous findings, it was advised to go for further radiologic imaging of spine by MRI in treatment-failure of functional urinary incontinence, unless patients have normal urodynamic findings.

Pippi Salle et al., evaluated 32 consecutive children with complicated enuresis who were referred for neurosurgical evaluation [22]. They recorded normal spinal MRI findings in 21 patients (91.3%), including 1 with a tethered cord and lipoma associated with a complex skeletal abnormality, and 1 with a nonprogressive, nonsurgical syrinx extending from T7 to T9 spinal levels. Only the case of lipoma required neurosurgical intervention. The authors concluded that MRI is of limited value in children with voiding dysfunction who have a normal neuro-orthopedic assessment, and that this modality should be reserved for those with associated neuro-orthopedic findings or complex skeletal deformity on plain x-ray(Pippi Salle, Capolicchio et al. 1998). In contrast, Arikan et al., investigated 81 children with voiding dysfunction and reported pathologic findings in 17 (38.6%) of 44 patients who had a normal neuro-orthopedic assessment [23]. They concluded that MRI of the lower spinal cord is a valuable tool for diagnosing occult spinal cord disorders, particularly in patients with the combination of voiding dysfunction refractory to conservative management and normal neurologic and orthopedic assessments.

Children who do not respond to behavioral or medical therapies for NNBSD should be considered candidates for invasive treatment modalities. Urinary incontinence is a very frequent problem encountered in pediatric urology outpatients. In our daily practice, most such children respond well to conservative methods such as timed voiding, behavioral modifications, biofeedback-coupled pelvic floor exercises, and anticholinergic agents. Schulman et al., found that conservative approaches were successful in 45% of 280 children with urinary incontinence [24]. The mean age of those patients who responded at presentation was 8.5 years, and the mean follow-up time was 22 months. Another study by Curran et al., revealed a similar cure rate of 43% among 30 patients with idiopathic detrusor overactivity. These authors described “complete resolution” in 87%; however, their definition of complete resolution included patients that were still on medication. Neither Schulman et al. nor Curran et al. were able to identify statistically significant clinical or urodynamic factors that predicted outcome [24, 25]. Weiner et al., reported a 60% treatment success rate after long-term follow up of children with daytime wetting [26].

Our study evaluated findings in children with tethered cord malformation. Such patients comprise a very small subset of many children who present with combination of

1. Does your child have urinary incontinence (peeing while not on the toilet) during the day?	No	Sometimes	1-2 times/day	3 or more times/day
	0	1	3	5
2. If Yes to Question 2	A few drops	Only underwear wet	Outer clothing layers wet	
	1	3	5	
3. Does your child have urinary incontinence (peeing while not on the toilet) during the night?	No	1-2 nights/week	3-5 nights/week	6-7 nights/week
	0	1	3	5
4. If Yes to Question 4 …	Underwear or pajamas wet		Bed wet	
	1		4	
5. My child goes to the toilet to pee …	Less than 7 times/day		7 or more times/day	
	0		1	
6. My child has to strain to pee.	No		Yes	
	0		3	
7. My child experiences pain when s/he pees.	No		Yes	
	0		1	
8. My child pees intermittently when on the toilet.	No		Yes	
	0		2	
9. My child has to go to revisit the toilet to pee soon after s/he pees.	No		Yes	
	0		2	
10. My child has to run to the toilet when s/he feels the need to pee.	No		Yes	
	0		1	
11. My child can hold his/her pee by crossing his/her legs, squatting, or doing the "pee dance."	No		Yes	
	0		2	
12. My child wets his/her clothes before reaching the toilet.	No		Yes	
	0		2	
13. My child does not pass stool every day.	No		Yes	
	0		2	
QUALITY OF LIFE				
If your child experiences any of the symptoms/issues mentioned above, does this affect his/her family life or social life?	Not at all	Sometimes	Seriously affects	
	0	1	5	

Figure 1: Pediatric Lower Urinary Tract Symptom Score (PLUTSS) [10]

treatment-resistant functional voiding problems and UUTD. Most patients who are resistant to treatment and have abnormal urodynamic findings have some degree of spinal pathology and should undergo MRI. These children require evaluation by a pediatric neurosurgeon [22, 23].

According to the current study, the treatment resistant disease should be followed carefully after untethering surgery because of continuing symptoms. In case of tethered cord malformation, the correction is effective for normalization of bladder dynamics. Hsihe et al., demonstrated that in children with abnormal urodynamics due to tethered cord malformation, untethering surgery may improve or even provides normalization of voiding dysfunction [27].

Stone et al., reported that children who presented with daytime wetting, uninhibited bladder contractions, and detrusor-sphincter dyssynergia were most likely to remain symptomatic after first line treatment. They offer that these patients might be considered for more aggressive alternative therapies, after a period of medical management [28]. In our series most of the treatment resistant children had DV scores different from the treatment responders' DV scores. In these cases main pathology was OAB.

The main factor for UUTD is having a reflux and high DLPP in our patient population. In our study, among patients who developed UUTD or patients with known but progressing UUTD, 4 had ongoing VUR and 8 had DLPP >20 cm H_2O in Group II. Among these patients the mean grade of VUR before treatment was 2.7 (min 2 max 4) in Group II and after treatment was 2.3 (min 1 max 4). It is well known that management of VUR in presence of disturbed bladder dynamics is a tough challenge. Seki et al., showed that factors such as low bladder compliance, presence of DSD and high maximum urethral closing pressure contributed to the incidence of VUR and were directly correlated with UUT damage [29].

Those patients also face a high number of UTI attacks and these attacks might affect the treatment response. Bael et al., described that urodynamics added little to the treatment of patients with OAB symptoms in the European Bladder Dysfunction Study [30]. The pre-treatment urodynamic variable "detrusor overactivity throughout filling" correlated in only 33% of patients with the clinical diagnosis of urge syndrome. This finding implied that 67% of the children with complaints of frequency, urgency, daytime wetting and holding maneuvers did not have overactivity of the detrusor in the filling phase. After treatment the prevalence of detrusor overactivity still was 27% but two-thirds of these patients did not have detrusor overactivity before treatment, and in fact exhibited detrusor overactivity de novo [30]. It means that detrusor overactivity did not correlate with treatment outcome. Clearly, in urge syndrome urodynamic variables do not follow clinical symptoms. We assume that urgency and frequency are due to overactivity, and start specific treatment based on that assumption. The assumption may be right but urge syndrome and concomitant detrusor overactivity may just occur on provocation only, giving rise to complaints and the seeking of medical attention when coping mechanisms fail. Because of the above mentioned reasons, some of the patients in the Group II had symptoms after successful surgery and they needed additional treatment. The response period for those patients may last as we expected.

High detrusor leak point pressure is shown to be a risk factor for UUTD in children with spinal dysraphism. Values higher than 40 cm H_2O are proven to be a major contribution to UUTD [31]. Even values between 20 and 40 cm H_2O are shown to be more sensitive for predicting UUTD [32]. In our study, the DLPP of children above 20 cm H_2O is related with UUTD which means determining the bladder urodynamic characteristics may be important in deciding emphasis of the treatment.

Thus, according to our results, treatment resistant children with abnormal spinal imaging have statistically more UUTD than children with treatment responders. More detailed randomized studies are needed to enlighten this situation.

Conclusion

Many normal children presenting with intractable voiding dysfunction fail to normalize with urotherapy and medical management. Those who are resistant to the treatment are candidates for UUTD. Those patients usually have concomitant VUR and high pressure bladder. In tethered cord patients, upper urinary tract damage is encountered more frequently than patients with treatment resistant cases.

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