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Impact of Bladder and Bowel Dysfunction in Children with Urinary Tract Infection: Morbidity and Outcomes

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Summary

Background: Bladder And Bowel(BBD) functions are closely related, and abnormalities in one system can affect the other. Further, the incidence of Urinary Tract Infection(UTI) and comorbidities is high and such patients thus require a multidisciplinary treatment approach.

Objective: This retrospective study aims to report the clinical BBD impact with their dynamic and morphology changes in the urinary tract, and present the outcomes with a comprehensive treatment.

Materials and methods: Among children aged 4-18 years with lower urinary tract dysfunction, 128 patients with filling and emptying bladder disorders associated with Functional Constipation(FC) and UTI, diagnosed by urodynamics and flowmetry, were included in this study. Children with anatomical or neurological anomaly were excluded. All the patients underwent ultrasonography, voiding urethrocystography, and DMSA scan to detect morphological changes. Patients were treated with urotherapy, bowel management, biofeedback, and transcutaneous electrical nerve stimulation. Drugs were administered on a case by case basis. Treatment outcome was assessed comparing symptoms, imaging, and functional records, at baseline and after ≥12 months of follow-up. According to International Children's Continence Society standardization, clinical outcome was classified as Complete Response (CR), partial response, or non-response.

Results: Among the 128 children included, 96% were female. Daytime wetting, urgency, and withholding maneuvers were the most frequent urinary symptoms. Vesicoureteral reflux (VUR) was observed in 28(22%) patients and renal scars in 54% of them. The CR rate of symptoms varied from 69 to 94%, 83% for UTI recurrence, and 70% for functional constipation. VUR resolution occurred in 65% of cases, with improvement in detrusor overactivity ($p<0.001$), voiding dysfunction ($p<0.0001$), and reduction of drug use ($p<0.001$).

Conclusions: BBD involving changes in filling and emptying bladder associated with FC causes high morbidity. Recurrent febrile UTI, VUR and renal scars are the main consequences and require comprehensive and prolonged treatment. A well-planned treatment strategy can improve symptoms, quality of life, VUR and prevents the occurrence or progression of kidney injuries.

Keywords: Children; Dysfunctional voiding; Functional constipation; Lower urinary tract dysfunction; Overactive bladder

Introduction

Bladder and bowel function are closely related and perform similar storage and emptying functions, and abnormalities in one system can affect the other [1]. Both systems share the same embryological origin, pelvic location, innervation, and passage through the pelvic floor musculature [2,3]. The pathophysiology of bladder and Bowel Dysfunction (BBD) is not fully understood but likely involves dysfunction of cortical control of Bladder efferent signals [4]. Many theories have been proposed regarding this interaction, such as a mechanical or sensor-neurological connection, or non-relaxation of pelvic floor muscles, all of which indicate the time required to restore normal functions, along with the need for more comprehensive therapy with an extended duration [3,5,6].

According to the International Children's Continence

Society (ICCS), the term BBD describes functional disorders of the bladder and the bowel [7]. These disorders include Detrusor Overactivity (DO) or underactivity, Voiding Dysfunction (VD), and Functional Constipation (FC), in the absence of anatomical or neurological abnormalities [8]. The incidence of BBD in childhood is unknown [4]. However, a systematic review reported that the prevalence of lower urinary tract symptoms in children with FC ranged from 37 to 64% in several studies [9]. BBD is often associated with UTI, Vesicoureteral Reflux (VUR), and renal scars [10]. Thus, children afflicted with BBD require a multidisciplinary treatment approach, and better success rates are obtained with long-term therapy [11]. These patients can benefit from cognitive-behavioral techniques, standard urotherapy, bowel management, pelvic floor biofeedback training, and Transcutaneous Electrical Nerve Stimulation (TENS). Pharmacological agents, including antibiotic prophylaxis, anticholinergics, and polyethylene glycol, are also typically administered. This study aimed to describe the morbidity and outcomes with comprehensive treatment in children with BBD and recurrent febrile UTI (Figure 1).

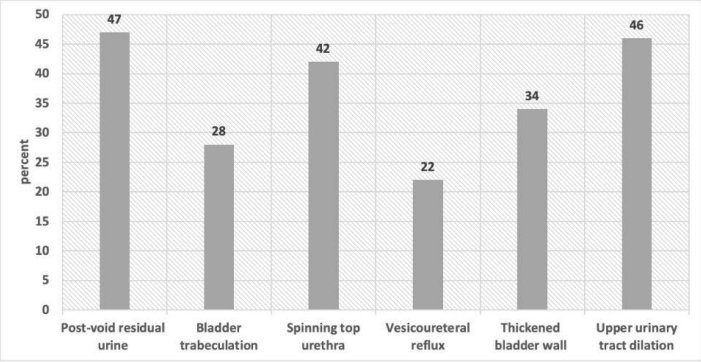

Figure 1: Changes in the urinary tract in children with BBD (N=128).

Methods

Patients

This retrospective study included 128 patients selected from the database of a reference center of BBD management. The inclusion criteria were children aged 4-18 years with UTI episodes, DO, VD, and FC. Children with an anatomical or neurological abnormality of the lower urinary tract, no history of UTI, incomplete assessment, non-adherence to treatment, or < 12 months of follow-up were excluded. The local Ethics Committee approved this study.

Assessment and Outcome

Children with lower urinary tract dysfunction were evaluated initially with standardized medical history; physical examination; bladder and bowel diaries; Bristol stool scale; Rome III criteria; and ultrasound examination of the kidneys and urinary tract. Terminology and classifications adopted by the ICCS standardization were used for diagnosis, procedures, and outcomes. DO and VD were diagnosed by flowmetry and Urodynamics (UD). Clinical outcome was classified as Complete Response (CR), defined as 100% symptom or disorder reduction; Partial Response (PR), defined as 50-99% reduction; or Non-Response (NR), defined as <50% reduction. FC was diagnosed according to the Bristol scale and ROMA IV criteria. Because of the dysfunction severity, all 128 children underwent UD concomitant to Voiding Urethrocystography (VCUG). A DMSA scintigraphy scan was performed in patients with VUR and recurrent febrile UTI. Treatment outcome was assessed by comparing the clinical, imaging, and functional evaluation records at baseline and after ≥12 months' follow-up.

Treatment

Patients underwent urotherapy consisting of a dietary orientation, adjustments to fluid intake, timed voiding regimens with or without a timer watch, records schedule, voiding posture, bowel management, support, and encouragement. At least ten biofeedback sessions with Electromyography (EMG) and flowmetry with the non-animated or animated device were performed. At least ten sessions of Transcutaneous Electrical Nerve Stimulation (TENS) were performed, with a pulse width of 250 μsec, a current frequency of 10 Hz, and intensity set at the sensory threshold with sacral or tibial transcutaneous electrodes. Anticholinergics were prescribed when marked detrusor overactivity was present. Laxatives were used when necessary.

Statistical analysis

GraphPad Prism®, version 6.0, was used for statistical analysis. Results are expressed as the mean and standard deviation for normally distributed data. A student's t-test was used for group comparison, and Fisher's exact test was used for group distribution comparison. Statistical significance was defined as $p<0.05$, and confidence intervals of 95%.

Results

Of 128 patients, 123 (96%) were girls, aged 4-18 years (mean age 7.2 years), and the mean follow-up period was 24.3±19.9 months. Daytime wetting, urgency, and withholding maneuvers were the most frequent urinary symptoms reported. With treatment, a significant improvement was observed in all symptoms ($p<0.0001$) (Table 1). The numbers of patients receiving each treatment are presented in Table 2. Functional and imaging evaluations at baseline and follow-up are described in Table 3. Spinning top urethra (42%), bladder trabeculation (28%), thickened bladder wall (34%), and post-void residual urine (47%), suggestive of functional obstruction related to voiding dysfunction, were observed at baseline. Significant improvements were noted with regards to thickened bladder wall ($p=0.0052$), flow shape

(p<0.0001), and post-void residual urine (p=0.0029). All patients presented with abnormal urine flow at baseline and 28% exhibited a bell-shaped flow pattern after 12 months' follow-up. Significant improvements were found in bladder compliance (p<0.0001) and the presence of detrusor overactivity (p<0.0001) between baseline and after 12 months' follow-up.

	Baseline symptoms n (%)	Response rate n (%)		
		CR	PR	NR
UTI	128 (100)	106 (83)	15 (12)	7 (5)
Constipation	128 (100)	90 (70)	31 (24)	7 (6)
Daytime wetting	103 (81)	79 (77)	21 (20)	3 (3)
Enuresis	59 (46)	41 (69)	13 (22)	5 (8)
Soiling	46 (36)	39 (85)	5 (11)	2 (4)
Urgency	97 (76)	81 (84)	11 (11)	5 (5)
Withholding manœuvres	109 (85)	98 (90)	9 (8)	2 (2)
Hematuria	16 (12.5)	15 (94)	1 (6)	0 (0)
Frequent voiding	37 (29)	36 (97)	1 (3)	0 (0)
Infrequent voiding	84 (66)	70 (83)	12 (15)	2 (2)
Abdominal pain	60 (47)	53 (89)	5 (8)	2 (3)
Vulvar erythema	88 (72)	69 (79)	18 (20)	1 (1)
CR= Complete Response, PR= Partial Response, NR= Non-Response				

Table 1: Clinical characteristics and outcome.

	Sessions, n	Patients, n (%)
Pelvic floor biofeedback	37.3 ± 20.4	128 (100)
Anorectal biofeedback	5.9 ± 2.8	31 (24)
Timer watch	-	54 (42)
TENS sessions	36 ± 19	128 (100)
Anticholinergics	-	109 (85)
Antibiotic prophylaxis	-	88 (69)
TENS = Transcutaneous Electrical Nerve Stimulation		

Table 2: Treatment procedures.

Imaging and functional assessment	Baseline		Outcome		p-value
	%	n/N	%	n/N	
Upper urinary tract dilation	46	59/128	-	-	-
Thickened bladder wall (≥3 mm)	34	35/102	14	14/86	0.0052
VUR (ureters)	15	37/240	5.4	13/240	0.0317
Spinning top urethra	42	50/120	-	-	-
Bladder trabeculation	28	34/120	-	-	-

Renal scars	35	22/62	35	22/62	-
Post-void residual urine >10% of BC	47	49/105	28	29/102	0.0029
Flow shape: Bell	0	0	28	36/128	<0.0001
Plateau	28	36/128	19.5	25/128	
Tower	52	66/128	51	65/128	
Staccato	20	26/128	1.5	2/128	
Detrusor uninhibited contractions (DO)	100	128/128	54	56/103	<0.0001
	Range	**Mean±SD**	**Range**	**Mean±SD**	
Cystometric capacity, mL (%EBC)	26-194	91±37	37-152	87±26	0.4145
Compliance, mL/cmH_2O	0.5-60	12.5±9.5	Jul-60	23±11	<0.0001
BC = Bladder Capacity (voiding volume + residual volume); VUR = Vesicoureteral Reflux; DO = Detrusor Overactivity; SD = Standard Deviation; %EBC = Bladder Capacity Expressed As The Percentage of Estimated Bladder Capacity					

Table 3: Functional and imaging changes between baseline and outcome.

At baseline, 28 (22%) patients had VUR. Among 37 refluxing ureters, the majority (89%) were assigned a baseline VUR grade of I-III: grade I = 15 (40%), grade II = 8 (22%), grade III = 10 (27%), grade IV = 3 (22%), and grade V= 1 (3%). After ≥12 months' follow-up, 24/37 ureters (65%) exhibited resolution, 10 (27%) exhibited reduced VUR, and 3 (8%) remained unchanged (p=0.0041). VUR resolution occurred in 93% of grade I, 63% of grade II, and 40% of grade III ureters. Among the three cases of grade IV VUR, all exhibited a downgrading. Only one patient had unilateral VUR grade V, and complete resolution occurred in this case. Renal scars were present in 22 (35%) of the 62 patients who underwent DMSA scanning (9 [41%] bilateral and 13 [59%] unilateral). Fifteen of these patients had VUR; hence, 54% of the VUR patient population had renal scars. Hypertension was found in 5% of patients (4 from 83 data recorded in the medical record). A significant reduction in anticholinergic and antibiotic use occurred. At baseline, 88 (69%) patients were receiving antibiotic prophylaxis, and at follow-up, this number had decreased to 38 (30%) (p<0.0001). Similarly, 109 (85%) patients were using anticholinergic drugs at baseline, but only 66 (52%) were at the end of follow-up (p<0.0001). Treatment adherence was classified as good in 76 (59%) of patients, acceptable in 38 (30%), and no adherence in 14 (11%).

Discussion

These results demonstrated that even dealing with severe cases of BBD, and most patients improved the symptoms after a comprehensive treatment, namely standard and specific urotherapy, anticholinergics, laxatives, and antibiotic prophylaxis. Nevertheless, we have learned that this takes time, and many are still in treatment. We noticed a significant reduction in the rate of UTI and the bladder and bowel symptoms. Our series is unique because all patients had BBD with documented disorders in bladder filling, bladder, and bowel emptying with recurrent ITU episodes. In the present study, the main reason for the first consultation was UTI recurrence. Although the children had a history of urinary and bowel symptoms, parents rarely recognized the correlation between events, particularly constipation, present in all cases. Therefore, it is essential to obtain a complete history of urinary and bowel habits in children with UTI, including bladder and bowel elimination patterns [4,12].

The most frequent symptoms associated with constipation were daytime incontinence, urgency, and withholding maneuvers, as observed in this population [13]. The reported prevalence of BBD in children with VUR is 34-70%. It has reported that BBD's presence reduces the surgical success rate for VUR and increases the febrile UTI rate after surgery; further, renal scarring is more likely in the patients with VUR, UTI, and BBD [12]. Dysfunctions unresolved in childhood persist into adulthood, with significant morbidity such as pyelonephritis, particularly during pregnancy [4]. A recent study demonstrated that 11 out of 20 children presented with high-grade VUR and Lower Urinary Tract Dysfunction (LUTD) during infancy were diagnosed with BBD at a mean age of 7.3 years, and most children were male [14]. In contrast, dilating reflux and female sex were identified as independent risk factors for BBD development [15]. In the current study, 96% of the children were female.

In this study, most VUR cases exhibited resolution or downgrading of VUR. VUR resolution occurred in 93% of grade I, 63% of grade II, and 40% of grade III ureters. The downgrading of VUR occurred in all grade IV ureters, and the only grade V

ureter exhibited resolution. Most authors agree that bladder dysfunction is highly suggestive of VUR persistence and reported that successful treatment of LUTD could resolve VUR [16,17]. Our results differ from other studies, with a higher VUR resolution rate, despite the severity of the dysfunction, probably correlated with individualized and comprehensive treatment, based on the intensity of changes in the bladder dynamics. Perhaps the BBD entity deserves a more precise stratification, according to severity and definition of the main dysfunction (filling or emptying), to indicate the best therapeutic plan. The prevalence of LUTD in children with VUR, in urodynamic studies, is higher than in non-urodynamic studies (38 to 75% and 18 to 50%, respectively) [18]. The assessment of the severity of the dysfunction and its response to treatment, only according to the symptoms, is very subjective [18].

Bowel dysfunction is reported in approximately 50% of children with LUTD and is more common in patients with VD [19]. BBD could be further improved with a better approach to constipation management, as described in the ICCS guidelines and other studies [5,8]. Constipation management must be the first step in the treatment of children with BBD [9]. Such management includes education; demystification; disimpaction with enema and laxatives; prevention of fecal re-accumulation with stool softeners, polyethylene glycol; and behavioral therapy. Long-term management and monitoring, often for months or years, is required [12]. Studies have reported the positive effects of parasacral TENS on constipation, in addition to an improvement in DO and post-void residual urine [20,21]. Clinically, one noted effect is the improvement of rectal sensation and evacuation [22]. It has been shown that TENS has no immediate effect on urodynamic parameters. Another advantage of using TENS in childhood compared to adulthood is the increase in neuroplasticity of the central and peripheral nervous systems with long-term effects [21]. Currently, TENS may be proposed as a first-choice therapy in children with BBD and is approved by the US Food and Drug Administration.

Anticholinergics may aggravate constipation and bladder emptying [4,12]. However, a low dose of anticholinergic, combined with TENS, can decrease the risk of PVR induced by oxybutynin [23]. Another disadvantage is the potential for relapse of DO when discontinuing the drug. In the current treatment protocol, low doses of anticholinergics were indicated, according to the intensity of the detrusor hyperactivity, in tandem with constipation treatment, urotherapy, biofeedback and TENS. The rate of anticholinergics uses decreased significantly, 85% at baseline and 35% at the end of the study. In the current patients, antibiotic prophylaxis was maintained until the patients exhibited improvement in LUTD and constipation. Despite controversies regarding the long-term use of prophylactic antibiotics, current guidelines recommend their use, mainly if VUR and renal scarring are present, which leads to significant UTI reduction [18]. The prophylactic use rate decreased significantly during treatment in the current patients (69% at baseline reduced to 30%). The BBD treatment approach involves cognitive-behavioral techniques. Urotherapy, which educates the patient and family of routine voiding and bowel habits, is particularly essential [4]. It teaches the child to live harmoniously with the dysfunction. It is recommended to avoid overdistension, adopt an adequate posture, and perform a double voiding maneuver. Although the value of a timed voiding schedule and adequate hydration is widely accepted, this is a demanding task for the child and depends heavily on maturation, motivation, and support from the parents and other adults. A multiple alarm watch increases adherence to the timed voiding regimen, with more efficient and lasting conditioning, and the relapse rate is low. The child becomes conditioned to voiding with regular intervals [24].

Biofeedback therapy is a non-invasive technique for treating pelvic floor dysfunction in children by utilizing EMG and flowmetry training. The benefit of biofeedback in children with VD has been reported in several studies [25,26]. Most of the patients in this study group underwent animated biofeedback with games, which can be more efficient due to higher interactivity [26]. However, a randomized study that compared the efficacy of animated and non-animated biofeedback reported no difference and suggested that the therapist's expertise seems to be more important than the device used [25,26]. In our practice experience, we have observed that the animated biofeedback is particularly interesting for younger children, as it can sustain their attention over a more extended period, making the session more efficient. In this study, 39% of patients had Spinning Top Urethra (STU), 28% had bladder trabeculation, and 46% had upper urinary dilation, suggesting the severity of VD. STU was related to recurrent UTI, VUR, poor bladder compliance, and more severe functional urinary obstruction [27]. The exact mechanism of STU is not well known; however, recurrent withholding maneuvers, in the presence of DO, may explain the inadequate relaxation of the pelvic floor with urethral dilation [27]. Patients who present with dyssynergic defecation, characterized by inadequate relaxation of the pelvic floor during defecation, benefit from Anorectal Biofeedback (AB) to teach children to relax and not squeeze the external anal sphincter during pseudo-defecation [28,29]. Dyssynergic defecation may be present in 50% of FC patients [5]. Among the patients in the current study, 31 (24%) had dyssynergic defecation and underwent AB, with a good result observed after only a few sessions.

Some secondary anatomical disorders, such as pelvic and ureteral dilation (46%), thickening of the bladder wall (34%), bladder trabeculation (28%), STU (42%), VUR (23%), and renal scars (35%), were found during this investigation. The presence of these comorbidities indicates the need for a comprehensive and prolonged treatment approach. One important finding is that there

was no progression of renal scaring during the study.

Most studies have reported the results of therapies based on symptoms. In the present study, an improvement in the symptoms was more significant than the normalization of UD parameters [30]. We believe that this indicates the necessity of a maintenance program throughout infancy in children with BBD, or until they become aware of their difficulties. This study has limitations related to its retrospective character. The combined treatment did not allow an analysis of the effect of each therapy separately. However, the severity of the dysfunction in this group of patients required a more comprehensive approach.

Conclusion

Early screening and active intervention for BBD are essential to preventing changes in the lower and upper urinary tracts resulting from dysfunction. An accurate diagnosis of the dysfunctional disorders and their impact on the upper urinary tract provides a better comprehension of the different therapeutic options. Combination therapy has yielded positive results in the long term. The nonpharmacological therapeutic modalities simultaneously improved bowel and bladder function, with no adverse effects and more permanent results, since the children learned to live with their dysfunction. Functional bladder and bowel disorders are common in children and involve extended treatment, often into adulthood. Thus, it is essential to develop educational programs that involve the entire family to guarantee lasting results. The main objectives of treatment are to improve functional obstruction and the associated consequences, thereby minimizing negative impacts on the kidneys and the quality of life of children and family members.

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