Impact of an interdisciplinary approach in children and adolescents with lower urinary tract dysfunction (LUTD)

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ABSTRACT

Introduction: The lower urinary tract dysfunction (LUTD) corresponds to changes in the filling or emptying of urine caused by neurogenic, anatomical and functional alterations. **Objective:** To evaluate the impact of treatment in children and adolescents with LUTD. **Methods:** Historical cohort of 15 year follow-up with the participation of 192 patients (123F, 69M), aged 0.1 to 16.8 years, analyzed at admission (T0) and at final follow-up (T1). Most patients belong to a neurologic bladder dysfunction group (60.4%). The treatment was uroterapy with behavioral and cognitive intervention, timed voiding, oral hydration, laxative diet, biofeedback, sacral nerve stimulation, clean intermittent catheterization (CIC), anticholinergic therapy, rectal enema, treatment of urinary tract infection (UTI) and, in refractory cases, surgical procedures such as continent and incontinent urinary diversion (vesicostomy), bladder augmentation and conduit for performing antegrade colonic enema. **Results:** The main symptoms were daytime urinary incontinence (82.3%), the non-monosymptomatic nocturnal enuresis (78.6%), fecal incontinence (54.2%) and constipation (47.9%). There was a significant reduction of urinary tract infection ($p = 0.0027$), daytime urinary incontinence ($p < 0.001$), nocturnal enuresis ($p < 0.001$), fecal incontinence ($p = 0.010$) and of vesicoureteral reflux ($p = 0.01$). There was significant increase in the use of CIC ($p = 0.021$), of anticholinergic therapy ($p < 0.001$) and decrease of chemoprophylaxis ($p < 0.001$). **Conclusion:** This study showed that treatment of LUTD in children must be individualized, and requires constant monitoring of clinical, laboratory and imaging to minimize the risk of kidney damage.

Keywords: bacteriuria; constipation; enuresis; intermittent urethral catheterization; urinary bladder, overactive; urinary bladder, neurogenic; urinary incontinence.

INTRODUCTION

Lower urinary tract dysfunction (LUTD) is an extremely complex condition. It involves multiple factors and processes that influence the storage or urine and micturition, including the bladder itself (smooth muscle, urothelium, connective tissue, and matrix), muscle contraction and the contractile system, humoral and endocrine messages, and, last but not least, the entire neuraxis from the postganglionic neurons through to the spinal cord, brain stem, and cerebral cortex.[1]

In LUTD, bladder filling and emptying may be affected by anatomical, neurological or functional alterations.[2] The quality of life of the individuals with this condition may be significantly impaired. Pediatric patients are particularly prone to developing emotional disorders when faced with urinary or fecal incontinence caused by loss of sphincter control. Children with LUTD suffer from low self-esteem, insecurity, anxiety, and decreased socialization, thus affecting their parents and family life.

Congenital malformations of the neural tube such as myelomeningocele, meningocele, and lipomeningocele are the most frequent causes of neurogenic bladder in children[3] and predispose patients to injuries of the upper urinary tract due to increased bladder pressure, detrusor-sphincter dyssynergia, post-void residual urine, and urinary tract infection with or without vesicoureteral reflux.[4] Thirty to 40% of the children with myelomeningocele develop some degree of renal dysfunction. This complication can be prevented or attenuated with appropriate treatment aimed at reducing bladder pressure and treating post-void residual urine.[5]

Children with untreated detrusor-sphincter dyssynergia develop upper urinary tract lesions, which may in some cases be present as early as in fetal life.[6] Children with neurogenic bladders must be followed in an outpatient regime since their first year of life, in order to detect the early signs of kidney involvement that may trigger the progression of chronic kidney disease.[7,8]

When LUTD has no neurological or anatomical cause, it is called urinary tract functional disorder, a condition believed to be related to genetic factors, neurological immaturity, inadequate sphincter training and voiding habits,[9-11] emotional problems, stress, sexual abuse, or unknown causes.[11]

The type of lower urinary tract dysfunction must be clearly identified before patients can be offered specific treatment. Interdisciplinary treatment should be directed to the preservation of renal function and improvement of urinary continence.[12]

This study aimed to assess the impact of treatment on patients treated at the LUTD Clinic followed up for 15 years.

Methods

This is a retrospective longitudinal observational epidemiological cohort study. The Research Ethics Committee of the institution approved the design of the study. Patients or their caregivers were asked to give informed consent before joining the study.

One hundred and ninety-two patients with LUTD of neurological and non-neurological causes submitted to workup were included in the study. Seventy-three were excluded for not meeting the enrollment criteria.

Clinically stable patients were scheduled to return to the LUTD Clinic every four or six months or within shorter time intervals when needed. The workup defined in the study protocol consisted of the following:

- Assessment of renal function on admission, annual urinalysis, and urine culture on every visit to the clinic.
- Renal ultrasound and voiding dynamics annually.[13]
- Voiding cystourethrography or radioisotope cystography and urodynamic test on admission for patients with neurological etiology LUTD and based on patient clinical evolution.
- Static renal scintigraphy on admission, repeated in the presence of changes in the initial examination.
- Dynamic renal scintigraphy upon signs of urinary obstruction.

Based on workup results, the treatment offered to LUTD patients consisted of the following:

Conservative treatment: anticholinergics, alpha-blockers, prophylactic chemotherapy, intestinal modulators, and clean intermittent catheterization (CIC).

Urotherapy and behavioral therapy including timed voiding, two-stage voiding, adequate fluid intake, laxative diet, voiding posture, voiding map, pelvic floor training using biofeedback or sacral nerve stimulation.

Surgery: incontinent (vesicostomy) or continent urinary diversion, bladder augmentation, and placement of an antegrade colonic conduit to allow rectal enemas to be carried out.

Patient clinical, workup, and imaging data were collected from their medical records. Patients were examined on admission (start time - T0) and on their last visit (finish time - T1).

The following parameters were assessed: daytime wetting, non-monosymptomatic nocturnal enuresis, constipation, fecal incontinence, urinary tract infection, asymptomatic bacteriuria, thickening of the bladder wall,

involuntary detrusor contractions, pelvic and/or calicial dilation, ureteral dilation, trabeculated bladder, bladder diverticulum, post-void residual urine, vesicoureteral reflux, and renal scarring.

Descriptive statistical analysis resorted to median, minimum and maximum values, and percent distribution of categorical variables to characterize the collected data. The results of the interventions performed in the LUTD Clinic were assessed. Clinical data and imaging parameters (ultrasound, radiology, and nuclear medicine images) captured on admission and at the end of follow-up were compared. The odds ratios of an event occurring at two different times (on admission and at the end of follow-up) were calculated. Statistical significance was attributed to differences between variables with a $p < 0.05$.

Results

The study included 192 patients (123 ♀, 69 ♂) with a median age of 6.6 (0.1 to 6.8) years followed up for a median of 4.9 (0.6 to 15.1) years.

The etiology of LUTD was mostly neurological (n = 16; 60.4%), with myelomeningocele (MMC) as the main diagnosis at baseline (n = 90; 77.6%) followed by sacral agenesis (n = 5; 4.3%), spine cord tumors (n = 4; 3.4%), and others. Most patients with MMC (70%) had hydrocephalus treated with ventriculoperitoneal (VP) shunts.

With respect to non-neurological etiologies, functional disorder (n = 46; 60.5%) and vesicoureteral reflux (VUR, n = 20; 26.3%) were the most prevalent causes of LUTD. Many of the patients with reflux had been diagnosed before they came to the Clinic. Renal function was normal in patients with LUTD regardless of etiology, with a median creatinine clearance of 138 (36.0 to 456.5) ml/min/1.73 m^2.

Table 1 shows that on admission the majority of the patients had daytime urinary incontinence and non-monosymptomatic nocturnal enuresis. Approximately half of the patients had constipation and fecal incontinence. Urinary tract infection occurred in 15% of the patients, whereas asymptomatic bacteriuria was more prevalent, affecting approximately a third of the enrolled individuals.

Imaging findings (Table 1) revealed that most patients had involuntary detrusor contractions and about half had ureteral dilation and post-void residual urine.

In terms of bladder emptying methods, 49 (25.5%) patients used clean intermittent catheterization, 93 (48.4%) resorted to chemoprophylaxis, and 139 (72.4%) did not take anticholinergics.

When surgery was considered, 14 patients (7.3%) had undergone incontinent urinary diversion procedures, three (1.6%) continent urinary diversion procedures, two (1.0%) had been submitted to bladder augmentation, and one (0.5%) had performed an antegrade colonic conduit procedure at T0. At T1, only eight patients (4.2%) had undergone incontinent urinary diversion, 11 (5.7%) continent urinary diversion, seven (3.6%) bladder augmentation, and four (2.1%) antegrade colonic conduit procedures.

Significant reductions in daytime urinary incontinence, non-monosymptomatic nocturnal enuresis, fecal incontinence, UTI, and VUR were observed at T1. Significant decreases were also seen in the use of chemoprophylaxis (OR = 0.20; $p < 0.001$), along with a significant increase in the use of anticholinergics (OR = 2.31; $p < 0.001$) and increased use of clean intermittent catheterization (OR = 1.67; $p = 0.021$). Pyelocaliceal and ureteral dilatation increased significantly. No alterations were seen in asymptomatic bacteriuria (Table 1).

Discussion

Analyzing the impact of treatment on patients is a way of understanding and evaluating whether the procedures adopted by the interdisciplinary team in the care of these patients are being effective or if they need to be replaced or complemented with other interventions.

Diurnal and nocturnal urinary incontinence are common clinical entities in pediatric urology, with prevalence ranging between 2% and 7% in children aged around seven years.[14] Leonardo *et al.*[15] studied children and adolescents with LUTD and reported daytime urinary incontinence rates of 88% among patients in the neurological

Table 1 Impact of treatment on clinical, workup, and imaging variables at T0 and T1

Variables	T0	T1	OR (5-95% CI)	*p*
Diurnal urinary incontinence				
Yes	158	112		
No	34	80	0.30 (0.18-0,48)	< 0.001
Nocturnal enuresis				
Yes	151	108		
No	41	84	0.46 (0.29-0.73)	< 0.001
Constipation				
Yes	92	82		
No	100	110	0.81 (0.54-1.21)	0.35
Fecal incontinence				
Yes	104	78		
No	88	114	0.58 (0.38-0.86)	0.010
Urinary infection				
Yes	28	12		
No	164	180	0.39 (0.19-0.79)	0.0027
Asymptomatic bacteriuria				
Yes	65	72		
No	127	120	1.17 (0.77-1.78)	0.53
Bladder wall thickening				
Yes	61	74		
No	131	118	1.34 (0.88-2.05)	0.205
Involuntary detrusor contraction				
Yes	133	120		
No	58	72	0.73 (0.47-1.11)	0.14
Pelvic and/or calicial dilation				
Yes	75	95		
No	117	97	1.53 (1.01-2.3)	0.04
Ureter dilation				
Yes	94	124		
No	98	68	1.9 (1.26-2.86)	0.002
Trabeculated bladder				
Yes	46	48		
No	143	141	1.05 (0.66-1.68)	0.81
Bladder diverticulum				
Yes	27	31		
No	165	157	1.2 (0.68-2.11)	0.60
Post-void urine residue				
Yes	92	87		
No	100	105	0.90 (0.60-1.34)	0.68
Vesicoureteral reflux				
Yes	57	37		
No	113	135	0.54 (0.33-0.88)	0.01
Renal scarring				
Yes	30	37		
No	162	155	1.28 (0.76-2.18)	0.34

Continued Table 1.

Chemoprophylaxis				
Yes	93	31		
No	99	161	0.20 (0.12-0.33)	< 0.001
Anticholinergics				
Yes	53	90		
No	139	102	2.31 (1.5-3.5)	< 0.001
Clean intermittent catheterization				
Yes	49	70		
Não	143	122	1.67 (1.08-2.6)	0.021

group and 73.6% in the non-neurological etiology group. In another study, daytime urinary incontinence was reported to have occurred in 60.9% of the patients with open and hidden spina bifida.[16]

Vasconcelos *et al.*[17] studied patients with refractory functional LUTD treated conventionally and found that 75% of the enrolled subjects had daytime urinary incontinence and 53.3% had non-monosymptomatic nocturnal enuresis, confirming the high frequency of occurrence of these symptoms.

Patients with LUTD are more exposed to the risks of having urinary tract infections due to the presence of post-void residual urine in their bladders and other urodynamic alterations. Transmural inflammation and fibrosis may further deteriorate the status of the bladder. LUTD has been associated high intravesical pressure and/or VUR and may cause acute pyelonephritis and renal injury. Patients with persistent relapsing UTI with fever - infants in particular - are more likely to develop renal scarring.[18,19] Therefore, UTI requires early aggressive treatment, as renal injury and failure are among its most serious complications. Early diagnosis and prompt treatment of UTI are part of the protocol in effect at our clinic designed to preserve patient renal function.

Since most patients in this study had neurogenic bladders accompanied by more complex urodynamic conditions and post-void residual urine volumes greater than 20 ml, the use of CIC was significantly increased (p = 0.021). The procedure - performed every three or four hours - may have contributed to significant reductions in the occurrence of UTI, daytime urinary incontinence, non-monosymptomatic nocturnal enuresis, and VUR. Other studies also reinforce the use of CIC in cases of incomplete voiding with significant levels of post-void residual urine[2,10] and neurogenic bladder.[20] A study carried out previously in our Clinic with patients on CIC described it as an effective procedure in promoting bladder emptying, reducing the occurrence of urinary infections even when the catheter was reused, and improving urinary continence despite the increase in cases of asymptomatic bacteriuria,[21] as described by other authors.[8,22] Many patients on CIC were able to be socially continent, without experiencing urine leakages between catheterizations. CIC training can be performed with the patient's caregiver - in most cases the subject's mother - or the child himself, when he shows interest in self-care and has no physical or cognitive limitations.

Asymptomatic bacteriuria was not a very prevalent condition in the two groups of patients at the time of admission, but it increased slightly at the end of the follow-up period (Table 1). This may be explained by the fact that CIC - often associated with asymptomatic bacteriuria - was prescribed at length for patients with post-void residual urine in their bladders. Patients on CIC are expected to have asymptomatic bacteriuria. As the procedure is clean but not sterile, inoculation of bacteria into the bladder is inevitable as the catheter is inserted.[23-27] Previous studies indicate that asymptomatic bacteriuria does not cause kidney injury,[15,28-30] and that antibiotics should not be prescribed to treat it, as such therapy could favor the selection of more pathogenic bacteria that could cause antimicrobial agent-resistant UTI.[24,27,28]

In this study, chemoprophylaxis at baseline was used by almost half of the patients. At the end of follow-up, the use of this therapy had significantly decreased. This finding can be clearly explained by the change in the approach adopted by the medical team treating the patients. The protocol currently in use at the LUTD Clinic is based on the literature and recommends chemoprophylaxis only for infants suffering from VUR or individuals with recurrent UTI for whom other causes of sustained infection have been ruled out.[30] According to Zegers *et al.*,[30] discontinuation of chemoprophylaxis in patients with neurogenic bladders and detrusor-sphincter dyssynergia on clean intermittent catheterization does not significantly increase the number of cases of UTI, showing that it should be discontinued as soon as specific treatment is instituted.

The reduction of vesicoureteral reflux may have been favored by a significant increase in the use of CIC in combination with anticholinergics (p = 0.0024), a drug class known to promote relaxation of the detrusor and produce bladder pressure decreases and increases in the compliance and capacity of the bladder.[27] Oxybutynin was the most frequently used anticholinergic drug in this study. It is an affordable medication - a characteristic that may increase compliance to treatment. Nevertheless, some patients experienced side effects previously reported in the literature,[20] the most common of which were flushing, dry mouth, dizziness, blurred vision. Patients with intolerance to oral oxybutynin on CIC were administered the drug through intravesical instillation, with satisfactory response. Bauer *et al.*[6] reported oral oxybutynin side effect incidences ranging from 6% to 57%; intravesical instillation of the drug decreased the incidence of side effects to nine percent. Other drugs were administered to non-catheterized patients.

CIC was not prescribed in the treatment of children with non-neurological etiology LUTD and post-void urine residues as their urethral sensitivity was preserved, thus hindering the acceptance of catheterization. The treatment of choice in these cases was urotherapy and behavioral therapy, with timed voiding and guidance on urination. Biofeedback and transcutaneous electrical nerve stimulation may also reduce incontinence in patients with functional lower urinary tract disorders. In a study also carried out in the LUTD Clinic, Vasconcelos *et al.*[17] used kinesiotherapy and biofeedback to reduce diurnal and nocturnal urinary symptoms. However, only patients undergoing biofeedback showed a significant reduction in post-void urine residues, probably due to improved relaxation of the pelvic floor muscles. Further corroborating this idea, Robson & Leung[31] prescribed urotherapy as the initial non-pharmacological intervention of choice particularly for patients with non-neurological conditions associated with urinary incontinence. This therapy takes three to six months and requires encouragement from parents, a motivated patient, and a caring family.

Constipation and/or fecal incontinence are often seen in patients with LUTD. Koff *et al.*[32] named the association between gastrointestinal and urinary disorders dysfunctional elimination syndrome (DES). Treatment of constipation is critical to the successful management of LUTD, although other authors have reported difficulties in achieving complete resolution of the gastrointestinal disorder.[33,34]

In this study, approximately half of the patients had fecal incontinence and constipation on admission (Table 1) - a pair of symptoms often described in the literature.[17,35] Fecal incontinence was significantly reduced at the end of the follow-up period. The gastrocolic reflex associated with the Valsalva maneuver may be used after bigger meals in an attempt to promote the elimination of feces in a toilet or potty, thus minimizing the inconveniences of the patient soiling himself. Other strategies are: laxative diets, increased water intake, proper posture during defecation with use of a footrest to ensure relaxation of the pelvic floor and aid in bladder and bowel emptying. Oral laxatives such as mineral oil, magnesium hydroxide, polyethylene glycol (PEG) without electrolytes, and lactulose[36] are introduced when these measures do not produce the desired result. Pashankar *et al.*[37] reported that 93% of the children treated with PEG went

on to have normal bowel habits and 52% ceased to suffer from encopresis.

Although reductions were seen in fecal incontinence, the same did not occur with constipation. Caregivers and school age/teenage patients fear that laxatives may decrease stool consistency and increase the occurrence of episodes of fecal incontinence. The potential exposure to embarrassing situations leads them to abandon treatment and deal with the troubles of hard and dry stool. Another point to be considered is that the diagnosis of constipation is often difficult, as it relies on information relayed by the caregiver and on the presence of a skilled interviewer. Although PEG without electrolytes has had excellent outcomes in the management of constipation,[11,38] the high cost of the treatment has limited its use to a smaller number of patients.

Loening-Baucke[35] confirmed the association between constipation and daytime urinary incontinence. The author reported a constipation resolution rate of 52% for patients enrolled in the study after the introduction of an aggressive treatment protocol. Improvements in daytime urinary incontinence were described for 89% of the individuals; 63% improved from nocturnal enuresis; and no more outbreaks of UTI were recorded.

In the LUTD Clinic, cases of chronic constipation refractory to behavioral or drug therapy, patients failing to comply with the prescribed treatment, and individuals with fecal incontinence are offered more aggressive therapies such as rectal enema. Patients with indication for bladder augmentation surgery are also offered antegrade colonic conduits to allow for enemas lasting 30 to 45 minutes with saline solution or tap water every two or three days to help empty their bowels.[20,27]

During the follow-up period only six patients underwent this procedure. All had neurogenic bladders and five were females; all acquired fecal continence. Another study with a seven-year follow-up reported this procedure was offered to six patients, all of whom with neurogenic bladders. The results were favorable, as fecal continence was achieved for five subjects and improvements in chronic constipation observed in all patients.[39]

Other surgical procedures are available when urotherapy and drug therapy cannot preserve renal function, prevent urinary infection, or maintain urinary continence. Incontinent urinary diversion has been indicated for patients unable to perform self-catheterization due to physical or mental limitations, for infants to whom urinary continence was not a social requirement, or when CIC could no longer be performed by the caregiver - usually the mother.[40] Another option is continent urinary diversion, in which the child or the caregiver empties the bladder by clean intermittent catheterization through a stoma reaching from the bladder to the anterior abdominal wall.[20] Bladder augmentation was recommended for patients with neurogenic bladders associated with detrusor hyperactivity, reduced bladder capacity, low bladder compliance, and high intravesical pressure not responding to conservative treatment and at imminent risk of injury to the upper urinary tract, with the purpose of enhancing bladder storage and decreasing intravesical pressure.[40]

Pyelocaliceal and ureter dilation were not quantified - they were considered as either present or absent - although they were mild in many patients. As the presence of pyelocaliceal and ureter dilation was associated with the development of renal scarring, we believe that detecting, quantifying, and controlling it is key to improve the management of kidney disease progression in our patients. Therefore, a more detailed categorization is needed, including mild, moderate, and severe levels of involvement.

Conclusion

Early detection of LUTD and diagnostic investigation with constant monitoring of clinical, workup, and imaging parameters are essential in preventing or minimizing alterations of the upper urinary tract and promoting urinary continence. Treatment must be individualized and delivered at an interdisciplinary specialized care center.

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