

## Original Article

# Usage of ultrasound indices in nocturnal enuresis treated with desmopressin therapy

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**Abstract:** Background: Nocturnal enuresis is a common problem in children and could be treated with desmopressin therapy. Here we assessed ultrasound indices affecting disease severity and treatment responses in candidates for pharmacotherapy for nocturnal enuresis. Methods: This prospective study was conducted in 2021-2022 on children diagnosed with nocturnal enuresis and candidates for desmopressin therapy. Demographic data of patients including age and gender were collected by a checklist. The severity of the disease was categorized into mild, moderate and severe. We measured the bladder volume index (BVI), bladder wall thickness (BT) and bladder volume wall thickness index (BVWI) by ultrasound. Patients were treated with desmopressin (administered 120 µg, stat and before sleeping) for 4 months and treatment responses were determined and compared. Results: In this study, data from 72 patients were analyzed. Complete response was achieved in 16 patients (22.2%), 25 patients (34.7%) had a good response to treatments, 18 patients (25%) had a partial response and 13 patients (18.1%) had no response. There was a significantly positive correlation between low and normal BVWI and the severity of the disease. Normal BVWI was found mostly in children with a mild degree of nocturnal enuresis; while low BVWI was associated with severe cases. There was a significant inverse correlation between response to treatment and bladder wall thickness. BVWI was significantly correlated with response to treatment. It was shown that 81.3% of children with complete responses and 76% of children with good responses had a normal BVWI, while 76.9% of children who showed no response to treatment had a low BVWI. Conclusion: BVWI and bladder wall thickness were significantly correlated with treatment response and BVWI had significant correlations with disease severity.

**Keywords:** Nocturnal enuresis, desmopressin, ultrasonography

## Introduction

Nocturnal enuresis affects almost 5-10% of children at the age of 7 years and is considered a prevalent disease [1, 2]. Nocturnal enuresis is a troubling condition for both children and their families. The diagnosis of temporal enuresis is that the child wets his or her clothes or bed at least twice a week for 3 consecutive months, or wets the bed in the form of a clinically important concern and discomfort in the child's life [3]. Enuresis can have significant psychological and emotional effects and severely affect the quality of life of their children [4]. Enuresis is the most common urological developmental disorder in children. Severe enuresis can continue imperceptibly with a prevalence of 2 to 3% in adulthood [5].

Treatment strategies for nocturnal enuresis include pharmacotherapies (including desmopressin and anticholinergics) and behavioral modifications [6]. Based on previous research, desmopressin with bed alarms could result in significant improvements [7]. The disadvantages of desmopressin treatment in children are not common. They include headaches, feeling sick, and mild tummy pain [6].

It has also been documented that increased bladder wall thickness significantly correlates with detrusor activity and predicts a good response to anticholinergics [8]. Furthermore, bladder capacity has a negative correlation with treatment responses [8, 9].

Measuring bladder indices with ultrasound could have high clinical values. The most used

indices include bladder volume index, bladder wall thickness and bladder volume wall thickness index. Recent studies suggested the use of bladder emptying efficiency (BEE) to determine the accuracy of bladder wall thickness measurements [9]. If BEE is less than 90%, patients are instructed to repeat voiding. Residual urine is then determined to assess bladder emptying efficiency (BEE)  $Z$  BVI pre-void - BVI post-void/BVI pre-void. If BEE is less than 90%, the child is asked to void again, as bladder thickness measurement is the least accurate when the bladder is full and most accurate when it is empty. The accuracy of bladder thickness measurements is higher when the bladder is empty [9, 10].

These measurements could be used widely and are non-invasive and highly reproducible. This study aims to evaluate the roles of the above-mentioned ultrasound indices in the severity of nocturnal enuresis and the prediction of response to desmopressin therapy.

### Methods and material

#### *Study design*

In this prospective cohort study, patients were entered from pediatric urology, general pediatric, and pediatric neurology clinics of hospitals, affiliated with the Isfahan University of Medical Sciences. The ethics code for this study was IR.MUI.MED.REC.1400.495. The clinical registry code for this study is: IR.ABADANUMS.REC.1392.201. This study was performed in 2021-2022 on patients with nocturnal enuresis.

#### *Inclusion and exclusion criteria*

The inclusion criteria were age 5-9 years old, enuresis at least once a week with complete continence during the daytime, intact neurologic and urologic physical examinations and signing the written informed consent by the parents or the guardian to participate in this study. The exclusion criteria were abnormal urological or neurological examinations, any other pharmacological treatments for nocturnal enuresis during the study course, bladder dysfunction during the daytime, any systemic conditions causing polyuria and lack of consent.

#### *Enuresis severity and bladder capacity*

Patients entered based on the mentioned criteria. Demographic data of patients including age and gender were collected by a checklist. We categorized the severity of enuresis according to the following criteria: mild enuresis was defined as enuresis 1-2 times/week, moderate enuresis was defined as 3-6 times/week and severe cases had 7 times/week. We predicted the patient's bladder capacity based on age as follows: Bladder capacity = (age \* 30) + 30 ml. This formula was described by Hjalmas and colleagues [8].

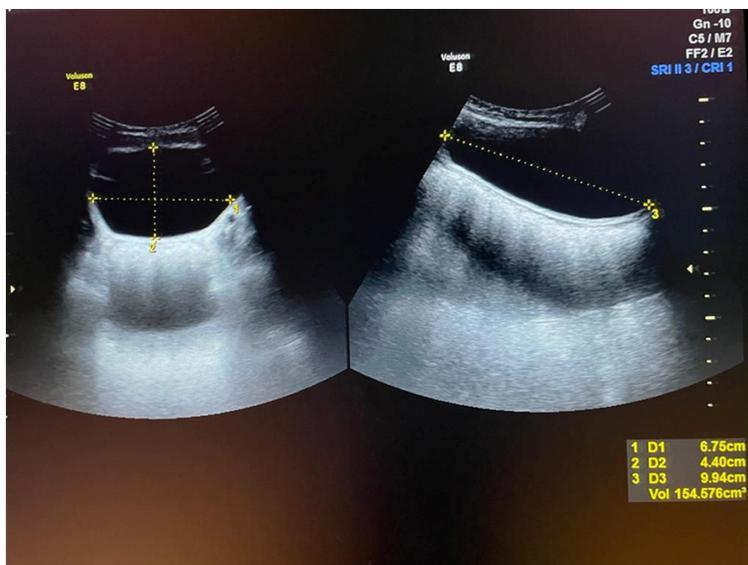
#### *Ultrasound measurements*

Ultrasound imaging of the patient's bladders was performed using ultrasound with 6.5 MHz and 12.5 MHz probes according to the patient's size (**Figure 1**). The bladder volume was measured after the patients were instructed to drink water to their tolerance. The bladder's maximal length, depth and width were measured in the longitudinal, anterior to the posterior surface and perpendicular to the depth of the bladder respectively. The bladder volume index (BVI) was calculated by multiplying the longitudinal, transverse and anteroposterior sections of the bladder. We considered a 70% safe zone for measured BVI and the predicted BVI. If the measured BVI was less than 70% of the expected amount, the child was instructed to drink more water or wait longer.

We measured the bladder wall thickness (BT) was measured from a zoomed image of the transverse plane of the voided bladder at three points, anterolateral, lateral and posterolateral, to avoid normal thickening of the anterior region at the urachal remnant and to avoid the posterior region as the trigone has a different structure to the rest of the bladder. Then the mean was calculated. Bladder volume wall thickness index (BVWI) was then calculated: BVWI measured BVI/measured BT. We measured BVWI and calculated measured BVI/measured BT. We also measured bladder emptying efficiency (BEE) to assess the efficacy of bladder thickness measurements.

#### *Interventions*

After primary ultrasound measurements, all patients were instructed to desmopressin ther-



**Figure 1.** Measurement of bladder volume and bladder wall thickness.

**Table 1.** Demographic characteristics of patients

Variable		Number	Percent
Age group (years)	5-6	31	43.1
	6-7	22	30.1
	7-8	12	17
	8-9	7	10
Gender	Male	39	54.2
	Female	33	45.8
Severity of nocturnal enuresis	Mild	24	33.4
	Moderate	30	41.7
	Severe	18	24.9
Response to treatment	No response	13	18.1
	Partial	18	25
	Good	25	34.7
	Complete	16	22.2

apy with an alarm system. Desmopressin was administered at 120 µg, stat, and before sleeping. Other treatments included toilet training, diet improvement and calcium and sodium-rich fluid restriction and are well described in previous studies [10, 11].

*Further measurements*

These treatments were conducted for 4 months. Patients were assessed at the end of treatments. Treatment response was considered as complete (no enuresis), good (more than 90% reduction in enuresis), partial (50%-90% reduction in enuresis) and no response

(less than 50% reduction in enuresis). Ultrasound measurements were performed again after treatments.

*Statistical analysis*

Data were collected and entered into the Statistical Package for Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL). Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage). Paired t-test, ANOVA test, and Chi-square were used to analyze the data. P-value <0.05 was considered as the significance threshold.

**Results**

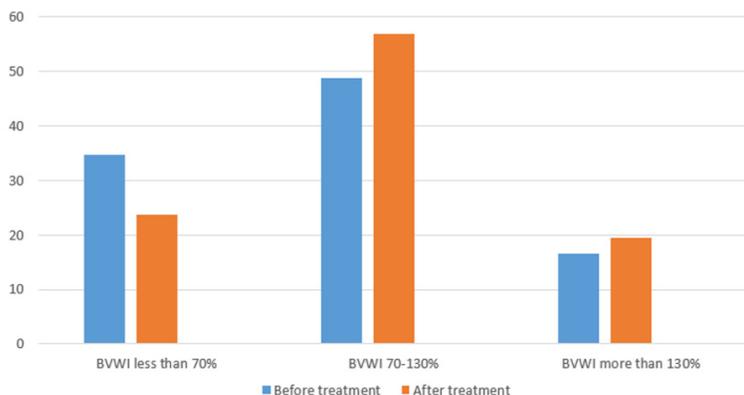
*Study population*

Totally, 118 patients were included based on the criteria. During the study, 46 patients were excluded and data from 72 patients were analyzed. Most cases were excluded due to lack of treatment compliance (30 patients, 65.2%) and receiving other types of treatments (14 patients, 30.4%).

*Demographic data*

The age distribution of the study population is summarized in **Table 1**. It was shown that 31 patients (43.1%) had 5-6 years, 22 patients (30.1%) had 6-7 years, 12 patients (16.6%) had 7-8 years and 7 patients (9.8%) had 8-9 years. The mean age of the patients was 6.37 ± 2.7 years. It is observed that 39 patients (54.2%) were male and 33 patients (45.8%) were female. Evaluation of the severity of nocturnal enuresis showed that 24 patients (33.4%) had mild, 30 patients (41.7%) had moderate, and 18 patients (24.9%) had severe forms of nocturnal enuresis. We assessed treatment responses in the study population. The data indicated that complete response was achieved in 16 patients (22.2%), 25 patients (34.7%) had a good response to treatments, 18

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**Figure 2.** Comparison of BVWI before and after treatments.

patients (25%) had a partial response and 13 patients (18.1%) had no response (**Table 1**).

### Bladder indices

We evaluated the bladder indexes of patients before treatments and compared the measurements to those after therapeutic management. Based on these data, the BVWI, bladder thickness, and bladder volume index improved significantly compared to before treatments ( $P < 0.05$  for all) (**Figure 2**). Based on our data, the number of patients with BVWI lower than 70% decreased significantly after treatments. On the other hand, the number of cases with BVWI between 70-130% and more than 130% increased after treatments ( $P = 0.012$ ). Furthermore, the bladder thickness significantly decreased ( $P < 0.001$ ) and the bladder volume index significantly increased after treatments ( $P < 0.001$ ) (**Table 2**).

### BVWI and treatment response

We observed that patients with complete and good responses had significant improvements in BVWI after treatments ( $P < 0.001$  for complete responses and  $P = 0.011$  for good responses). These data are shown in **Table 3** and **Figure 3**.

### BVWI and disease severity

We observed no significant correlations between the severity of enuresis with age and sex. We observed a significant positive correlation between bladder wall thickness and the severity of enuresis. There was a significantly positive correlation between low and normal

BVWI and the severity of the disease. Normal BVWI was found mostly in children with a mild degree of nocturnal enuresis (75% of mild cases had normal BVWI), while low BVWI was associated with severe cases (77.7% of severe cases had low BVWI). High BVWI was not significantly correlated with severity. These data are shown in **Table 4**.

### BVWI and treatment responses

We also assessed the factors associated with response to desmopressin therapy. We observed no significant correlations between age and gender with the response. There was a significant inverse correlation between response to treatment and bladder wall thickness; meaning the best responses were observed in cases with lower bladder wall thickness. BVWI was also significantly correlated with response to treatment. It was shown that 81.3% of children with complete responses and 76% of children with good responses had a normal BVWI, while 76.9% of children who showed no response to treatment had a low BVWI (**Table 5**).

## Discussion

In this research, we evaluated different ultrasound indices to assess the severity of nocturnal enuresis and prediction of response to desmopressin therapy. The results of this study indicated that there was a significantly positive correlation between low and normal BVWI and the severity of the disease. Normal BVWI was found mostly in children with a mild degree of nocturnal enuresis; while low BVWI was associated with severe cases. Furthermore, it was shown that there was a significant inverse correlation between response to treatment and bladder wall thickness; meaning the best responses were observed in cases with lower bladder wall thickness.

Our data also showed that BVWI was significantly correlated with response to treatment. Ultrasound-measured bladder wall thickness and BVWI are strongly associated with the severity of nocturnal enuresis and are highly predictive of treatment response to behavioral

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**Table 2.** Comparison of different ultrasound indexes among patients

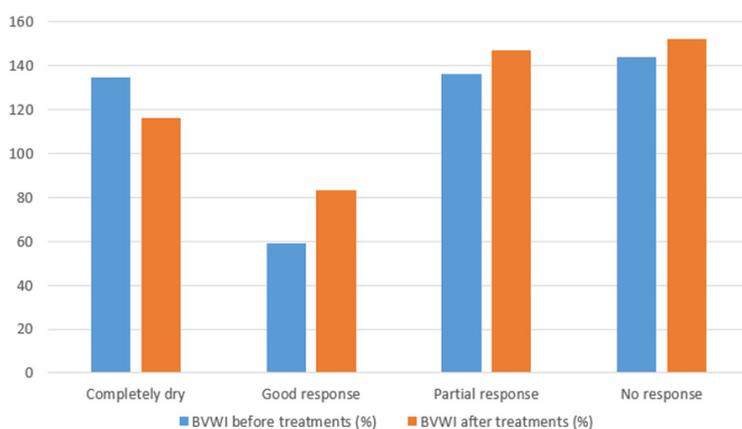
Variable		Before treatment	After treatment	P value*
BVWI (N (%))	Less than 70%	25 (34.7%)	17 (23.6%)	0.012
	70-130%	35 (48.7%)	41 (56.9%)	
	More than 130%	12 (16.6%)	14 (19.5%)	
Bladder thickness		0.4232 ± 0.15	0.3622 ± 0.063	<0.001
Bladder volume index		453.30 ± 133.6	648.21 ± 147.57	<0.001

\*Paired t-test.

**Table 3.** Comparison of BVWI in patients based on their outcomes

Treatment outcome	Number of patients	BVWI before treatments (%)	BVWI after treatments (%)	% change	P-value*
Completely dry	16	134.7 ± 48.7	116.3 ± 8.9	38.1 ± 10.6	<0.001
Good response	25	59.3 ± 44.2	83.5 ± 44.8	27.6 ± 8.4	0.011
Partial response	18	136.6 ± 62.9	147.3 ± 52.6	12.3 ± 6.6	0.095
No response	13	144.5 ± 57.4	152.0 ± 55.9	8.3 ± 4.7	0.334

\*Paired t-test.



**Figure 3.** Comparison of BVWI based on treatment response.

therapy. Previous studies also support the use of ultrasound in measuring bladder wall thickness [8]. It was shown in this study that the treatment responses could be predicted based on bladder wall thickness and BVWI. It was shown that 81.3% of children with complete responses and 76% of children with good responses had a normal BVWI, while 76.9% of children who showed no response to treatment had a low BVWI. It also was indicated that patients with complete and good responses had significant improvements in BVWI compared to other patients.

There have been different researches in the past on the values of bladder volume, bladder wall thickness and BVWI in the response of

nocturnal enuresis to drug therapy. Only limited studies have assessed these indices in our region [12]. It has been documented that pharmacotherapies have higher success rates but also high risks of relapse in children [13]. These data could support the careful use of desmopressin treatments in clinical practice. In the present study, we achieved complete responses in 22.2% of patients and good responses in 34.7% of patients.

Our results could be compared to some previous studies. A similar study was conducted in 2012 by Elsayed and colleagues in Egypt. In this study, 74 children with nocturnal enuresis were entered. After behavioral therapies, they showed that low and normal BVWI had positive correlations with disease severity and normal BVWI was associated with better responses to treatments [14]. In 2018, a study was performed by Hamidreza Qashqai and colleagues in Iran on 259 children with enuresis. This study evaluated the urodynamic and ultrasound findings in patients after 6 months of treatments with desmopressin and behavioral therapies. The results indicated that normal BVWI (30-70%) was seen in most patients with a proper response to treatments and abnormal parameters were found mostly in patients with no

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**Table 4.** Assessment of factors that predict severity of disease

Variable	Mild (N = 24)		Moderate (N = 30)		Severe (N = 18)		P-value	
	N	%	N	%	N	%		
Age (years)	5-6	10	41.6	13	43.3	7	38.8	0.359*
	6-7	6	25	9	30	5	27.8	0.382*
	7-8	4	16.7	5	16.7	4	22.2	0.475*
	8-9	4	16.7	3	10	2	11.2	0.238*
Gender	Male	14	58.3	17	56.7	9	50	0.314*
	Female	10	41.7	13	43.3	9	50	0.162*
Bladder volume (mean ± SD)		81.33 ± 12.51		83.14 ± 12.40		84.02 ± 11.23		0.684**
Bladder wall thickness (mean ± SD)		4.51 ± 0.38		5.52 ± 0.83		6.38 ± 0.86		<0.001**
BVWI	Low	3	12.5	9	30	14	77.8	0.001*
	Normal	18	75	14	46.6	2	11.1	<0.001*
	High	3	12.5	7	23.4	2	11.1	0.133*

\*Using Chi Square test, \*\*Using ANOVA test.

**Table 5.** Factors associated with response to treatment

Variable	No response (N = 13)		Partial (N = 18)		Good (N = 25)		Complete (N = 16)		P-value	
	N	%	N	%	N	%	N	%		
Age (years)	5-6	6	46.2	9	50	12	48	7	43.8	0.266*
	6-7	3	23.2	4	22.2	5	20	4	25	0.348*
	7-8	2	15.3	4	22.2	4	16	2	12.5	0.420*
	8-9	2	15.3	1	5.6	4	16	3	18.7	0.618*
Gender	Male	5	38.4	13	72.2	14	56	7	43.8	0.441*
	Female	8	61.6	5	27.8	11	44	9	56.2	0.652*
Bladder volume (mean ± SD)		80.12 ± 12.51		82.05 ± 11.48		84.05 ± 11.28		85.86 ± 12.60		0.377**
Bladder wall thickness (mean ± SD)		6.51 ± 0.62		5.92 ± 0.73		4.62 ± 0.58		4.28 ± 0.27		0.001**
BVWI	Low	10	76.9	11	61.2	3	12	2	12.5	<0.001*
	Normal	1	7.7	1	5.5	19	76	13	81.2	0.023*
	High	2	15.4	6	33.3	3	12	1	6.3	0.014*

\*Using Chi Square test, \*\*Using ANOVA test.

treatment responses. It was also reported that the bladder volume index was higher in patients with a proper response to treatments [15]. These data were consistent with our findings.

In another study by Siroosbakht and others in 2018, 102 children with urinary problems were evaluated by ultrasound. This study highlighted the use of BVWI in the follow-up of patients. Based on the reports, increased bladder wall thickness was observed in more than half of children with enuresis. It was also suggested that BVWI measurements should be used in enuresis [16]. A recent study was performed by Caswell and colleagues in 2020 on the use of ultrasound in nocturnal enuresis. Based on the results of this study, measurements of bladder

wall thickness and bladder volume index could be useful in both diagnosis of bladder problems and also assessments of response to treatments and suggested that further studies should be conducted in this regard [17]. The results of our study were in line with these previous research. We also showed that BVWI measurements and ultrasound indices could have predictive values for treatment responses.

A survey was conducted by Hooman and colleagues in 2011. This study assessed the bladder ultrasound indices and treatment responses in 122 children with urinary complaints. The results of this study revealed that the frequency of thick, thin, and normal BVWIs did not differ

significantly between patients and controls [18]. These data were not in line with our findings. The main reason could be differences in patient characteristics between previous research and the methods of treatments. In the present study, we evaluated the treatment response predictors for desmopressin therapy while most previous research has assessed pharmacotherapies.

The use of ultrasound is convenient and non-invasive. This method could provide valuable information before treatments. Children with nocturnal enuresis could be evaluated with ultrasound before treatments and desmopressin could be considered suitable for some candidates based on their ultrasound indices.

The limitations of this study included a restricted study population and not comparing our results with other treatment methods including behavioral treatments. We recommend that further studies should be conducted in this regard.

### Conclusion

In this study, a complete response to desmopressin therapy was achieved in complete response in 22.2% of patients. We observed that BVWI and bladder wall thickness were significantly correlated with treatment response and BVWI had significant correlations with disease severity. Ultrasound assessments could give valuable clinical data and could be used to determine treatment options.

### Disclosure of conflict of interest

None.

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### References

- [1] Walker RA. Nocturnal enuresis. *Prim Care* 2019; 46: 243-248.
- [2] Tsuji S, Takewa R, Ohnuma C, Kimata T, Yamanouchi S and Kaneko K. Nocturnal enuresis and poor sleep quality. *Pediatr Int* 2018; 60: 1020-1023.
- [3] Sarici H, Telli O, Ozgur BC, Demirbas A, Ozgur S and Karagoz MA. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. *J Pediatr Urol* 2016; 12: 159, e1-6.
- [4] Hamed A, Yousf F and Hussein MM. Prevalence of nocturnal enuresis and related risk factors in school-age children in Egypt: an epidemiological study. *World J Urol* 2017; 35: 459-465.
- [5] Torkashvand F, Rezaeian M, Bagheani T, Zarafshan H, Mostafavi SA and Bidaki R. Prevalence of nocturnal enuresis in school-age children in Rafsanjan. *Pediatr Nephrol* 2015; 3: 71-74.
- [6] Saroukhani A and Zadeh AR. Incidence of steal syndrome following arteriovenous fistula and arteriovenous graft. *Int J Burn Trauma* 2022; 12: 121.
- [7] Nield LS, Nease EK and Grossman OK. Enuresis management in the primary care pediatrics clinic. *Pediatr Ann* 2018; 47: e390-e395.
- [8] Yu PH, Lin CC, Fan YH, Lin AT and Huang WJ. Correlations between bladder wall thickness and clinical manifestations in female patients with detrusor underactivity and detrusor overactivity-with-detrusor underactivity. *J Chin Med Assoc* 2021; 84: 937-941.
- [9] Lo PF, Chang WH and Wang PH. Is ultrasound valuable for the diagnosis of women with abnormal detrusor activity? *J Chin Med Assoc* 2022; 85: 3-4.
- [10] Farsani DM, Rafieezadeh A, Nourian N, Mohammadi H, Naghibi K and Saghir K. Evaluating the preventive effect of metoclopramide and aminophylline on pain after deep vitrectomy. *Int J Physiol Pathophysiol Pharmacol* 2022; 14: 316.
- [11] Ouyang Z, Sperry ZJ, Barrera ND and Bruns TM. Real-time bladder pressure estimation for closed-loop control in a detrusor overactivity model. *IEEE Trans Neural Syst Rehabil Eng* 2019; 27: 1209-1216.
- [12] Hussong J, Mattheus H, Wachs S, Equit M and von Gontard A. Evaluation of a bladder and bowel training program for therapy-resistant children with incontinence. *J Pediatr Urol* 2021; 17: 302.e1-302.e8.
- [13] von Gontard A and Kuwertz-Brörking E. The diagnosis and treatment of enuresis and functional daytime urinary incontinence. *Dtsch Arztebl Int* 2019; 116: 279-285.
- [14] Farsani DM, Nikkhoo I, Zadeh AR, Nourian N and Montazeri K. Effect of aminophylline, ketamine and paracetamol on pain intensity after deep vitrectomy surgery. *Int J Physiol Pathophysiol Pharmacol* 2022; 14: 289.
- [15] Khanna K, Agarwala S, Bakhshi S, Srinivas M, Jana M, Devasenathipathy K, Bajpai M and Bhatnagar V. Need for urodynamic evaluation as a regular follow-up tool in assessment of long-term urological outcomes in patients with

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- sacrococcygeal teratoma. *J Pediatr Surg* 2019; 54: 2107-2111.
- [16] Ghobrial EE, Fawzi NM, Shiba MF and Tawfik MA. Abdomino-pelvic ultrasound evaluation in monosymptomatic primary nocturnal enuresis. *Clin Pediatr (Phila)* 2023; 62: 33-38.
- [17] Caswell N, Kuru K, Ansell D, Jones MJ, Watkinson BJ, Leather P, Lancaster A, Sugden P, Briggs E, Davies C, Oh C, Bennett K and DeGoede C. Patient engagement in medical device design: refining the essential attributes of a wearable, pre-void, ultrasound alarm for nocturnal enuresis. *Pharmaceut Med* 2020; 34: 39-48.
- [18] Hooman N, Hallaji F, Mostafavi SH, Mohsenifar S, Otukesh H and Moradi-Lakeh M. Correlation between lower urinary tract scoring system, behavior check list, and bladder sonography in children with lower urinary tract symptoms. *Korean J Urol* 2011; 52: 210-215.