



Treatment of lower urinary tract dysfunction facilitates awakening and affects the cure rate in patients with nonmonosymptomatic enuresis

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Purpose: Poor awakening in patients with enuresis has been assumed to be an adaptation to the chronic influence of arousal stimuli like lower urinary tract dysfunction (LUTD). This study aimed to examine the effect of controlling LUTD on improvement of awakening and cure of enuresis.

Materials and Methods: Data for 119 enuretic patients with overactive bladder were retrospectively analyzed. The patients received urotherapy, laxatives, and anticholinergic agents. LUTD symptoms and enuresis were regularly monitored every 3 months. History of waking up because of bedwetting (ability to awaken, AA) was used as a surrogate marker of arousal and was graded at baseline and every 3 months of treatment. Changing distribution of each grade of AA was associated with other LUTD symptoms. Multivariate analysis was applied to understand whether the lack of improvement in AA might harbor any prognostic implications regarding cure of enuresis.

Results: Decreasing number of LUTD with treatment corresponded to increasing number of better AA. Enuresis was resolved completely in 88 patients in a median time of 7 months. Failure to show even single episode of awakening before bedwetting within 6 months of treatment and persistent daytime incontinence were identified as risk factors for treatment resistance until 18 months of treatment.

Conclusions: Controlling LUTD symptoms in the management of nonmonosymptomatic enuresis was crucial for not only the treatment of enuresis but also for allowing the patients to obtain better arousal. AA tended to improve subsequent to bladder control and may contribute to the cure of enuresis.

Keywords: Arousal; Cure; Enuresis; Urinary bladder

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INTRODUCTION

Accumulating evidence suggests that sleep problems in enuresis may in fact lie in problems of arousal rather than

in sleep itself [1-4]. Current hypotheses highlight the role of various stimulators in affecting arousal during sleep, such as periodic limb movements [1], sleep-disordered breathing [5], nocturnal polyuria [6], and autonomic imbalance [7], which

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may hamper the transition from light to deep sleep and thus lead to chronic sleep deprivation [3,4]. When these stimulators are present in those whose brain areas for bladder control are not sufficiently mature, the arousal threshold appears to be elevated as a compensatory measure for deprived deep sleep. This makes the patient unable to wake up to the sense of micturition [8-11]. Supporting this hypothesis, treating nocturnal polyuria was found to improve sleep, leading to better arousal [6].

Likewise, bladder contraction is also presumed to be a strong stimulus for arousal. The presence of detrusor overactivity is detrimental to sleep transition into deep sleep and may inhibit arousal and inhibit awakening in enuretic patients. This was suggested in a polysomnography study which revealed an association between sleep, arousal problems, and bladder dysfunction in enuretic children [3]. If this is true, the assumption of “bladder-brain dialogue,” which indicates the reciprocal interaction of the brain with the bladder, makes sense and may challenge the presumption of a unidirectional effect of the brain on the bladder. Provided that impaired bladder function may be able to hamper brain function, improvement of bladder control is expected to change brain function leading to better arousal.

Thus, the main objective of this observational study was to assess whether better arousal occurs after treatment of lower urinary tract dysfunction (LUTD) and control of daytime symptoms. To prove this hypothesis, we would need a complicated sleep study, such as polysomnography, to evaluate arousal, which is virtually impossible in clinical practice. As an alternative, we developed a clinical proxy of arousal, ability to awaken (AA) based on history of awakening around bedwetting. We found that patients with good clinical courses were awakening better. That is, patients who had not been able to wake up with their underwear soaked became awakened with the sense of wet undergarments and then were finally awakening even before wetting.

This study was conducted in patients with nonmonosymptomatic enuresis (NME) [12] with concomitant symptoms of LUTD. Given that the reported prevalence of bladder dysfunction manifested by LUTD symptoms among enuretic patients ranges widely from 21% to 99% [13-15], this population is one of the majorities that would be encountered in the clinic. In addition, these patients are more likely to have a prolonged course and have been observed to even become resistant to treatment if NME is treated like monosymptomatic enuresis (ME) [16-18].

If AA, the surrogate marker for arousal, could be improved by the control of LUTD, we proposed this improved arousal may indicate the successful transition from NME

to ME, which is a required step for the successful control of NME. Given the relatively good prognosis of ME in favor of NME [19], a sign of better AA during sleep may help to predict good prognosis. Hence, another objective of this study was to show whether the resolution of enuresis was related to obtaining AA. To reveal this relationship, we compared the rate and time course of resolution of enuresis between those who achieved early AA and those who did not.

MATERIALS AND METHODS

1. Criteria for enrollment

This was retrospective observational study and the review of data was approved by institutional review board. The diagnosis of NME was based on a positive history for LUTD symptoms, which was revealed in the Dysfunctional Voiding and Incontinence Symptom Score (DVISS) [20]. Further urodynamic classification of LUTD, a 2-day voiding diary, uroflowmetry with concomitant electromyography, and measurement of postvoid residual urine (PVR) volume was also applied to all patients. Since this study was intended to homogenize the patient population into cases of overactive bladder (OAB), data that did not fulfill the following criteria for OAB were excluded from review: 1) positive history for urgency and/or urge incontinence, 2) bell or tower-shaped uroflowmetry results, 3) normal PVR volume. Constipation was diagnosed when there were more than 2 affirmative answers to the ROME III criteria. Patients had to be naïve to previous anticholinergic medications.

Patients with moderate to severe enuresis, for which episodes occurred at least three times a week, were enrolled. No data for patients with any history of anatomical abnormalities in the urinary tract or neuropathic bladder were included for review.

2. Determination of ability to awaken

As a qualitative alternative to a sleep study, we developed a subjective grading measure of awakening status based on parental reporting. This grading was derived from our clinical observation that improvement of enuresis is often accompanied by increased awakening episodes, which suggests improved arousal. We qualitatively classified awakening episodes into 3 grades as a surrogate marker of arousal, although this classification is not validated by objective methods for arousal grading. We titled this grading as the AA. To encourage parental motivation to give information on AA during follow-up, the potential implications of AA in control of LUTD and resolution of enuresis were sufficiently explained during the patients' first visit. We asked patients

or parents to grade their current status during the last month and whether any improvement of AA occurred at each follow-up. Depending on the presence and time of signs of awakening, three semi-qualitative grades were employed: Grade 1: state of waking up before bedwetting. Grade 2: state of waking up after bedwetting. Grade 3: state of no awakening around bedwetting.

In grade 1, which is the final stage of awakening, patients were sure that they were awakened by the sense of bladder filling and never failed to hold urination until they reached the toilet. Improvement in AA was defined when even a single episode suggestive of a better AA grade was observed.

3. Treatment protocol

As per the International Children's Continence Society (ICCS) recommendation, the treatment protocol managed constipation first followed by LUTD and then nocturnal enuresis. Hence, all children initially received standard urotherapy for 4 weeks. In cases where the presence of constipation was suspected by more than two positive responses to ROME III, polyethylene glycol was concurrently prescribed to enhance bowel disimpaction. If there was no subjective improvement within 4 weeks of standard urotherapy and/or treatment of constipation, patients received solifenacin acetate (5 mg/day) along with the aforementioned treatment. If there was no effect on the bladder diary for 3 months, titration of 10 mg/day was attempted to ensure better bladder control. The use of desmopressin was deferred until there was at least a partial response in terms of improvement of daytime symptoms. Patients were followed at intervals of every 3 months with the DVISS, bladder diary, and questions about newly found changes in AA. Quitting drug treatment was considered when there was enuresis of less than 1 episode during the 3 months of follow-up, without further evidence of persistent daytime symptoms and constipation.

4. Assessment of responses and statistical analysis

In accordance with the ICCS, the recommended responses to treatment were assessed by using the aforementioned questionnaire and voiding diary [12]. All patients were reported to have urgency and small-volume episodes in voided volume. The severity of urgency was not described well in the DVISS. Hence, we asked the patients or parents to measure the degree of urgency on a percent scale at each visit. The number of small-volume episodes on the voided volume chart was another measure. Thus, we tried to take the two together and calculate the average in determining responses.

Quantitative data of the groups were presented as means with standard deviations and qualitative data as numbers and percentages. The chi-square test and standard t-test were used for comparisons of differences between categorical and quantitative variables, respectively. The changing distributions of LUTD symptoms, grade 3 AA, and enuresis were plotted on time scales and their slopes were assessed by linear regression to compare their pattern of changes. The time to complete resolution (CR) was plotted against time, and Kaplan–Meier analysis was applied to reveal the time course of cure after 6 months of treatment. All analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, USA) and the assumption of slope was performed using linear regression in GraphPad PRISM (ver. 6). A value of $p < 0.05$ was considered significant.

RESULTS

Our enuresis patient cohort included 255 children with primary enuresis who were treated between 2013 and 2016. Of them, 73 patients with ME, 35 with incomplete data for awakening history during bedwetting, and 5 patients with sphincteric incontinence revealed in urodynamics were excluded. The data for 23 patients who showed dysfunctional voiding during repeat uroflowmetry-electromyography study were additionally excluded from review as they received standard urotherapy and biofeedback for pelvic floor muscle exercise. In all, 119 patients with OAB who received standard urotherapy, management of constipation, and anticholinergic agents for their NME and whose data for awakening were available through 1 year of follow-up were analyzed.

The demographic characteristics of the patients are summarized in Table 1. More than two-thirds were boys, and three-quarters wet their bed nearly every day. Urgency and urgency incontinence were reported by all and by 49 patients (41.2%) on the DVISS, respectively. Constipation based on the ROME III criteria or distal faecal impaction was identified in 37 patients (31.1%). The mean maximal voided volume by bladder diary was 168 mL, corresponding to 68% of the age-adjusted bladder capacity [12]. Uroflowmetry revealed bell and tower shapes in 62 (52.1%) and 57 (47.9%) patients, respectively. Increased PVR (more than 20 mL) was found in 4 patients (3.4%).

Treatments (1 month) of standard urotherapy only and standard urotherapy and polyethylene glycol were applied in 82 and 37 patients, respectively. Treatment of constipation was determined by more than 2 positive responses on the ROME III criteria. Although this treatment resulted in the improvement of daytime symptoms and enuresis in 33 (27.7%)

Table 1. Clinical features of 119 children with nonmonosymptomatic enuresis (n=119)

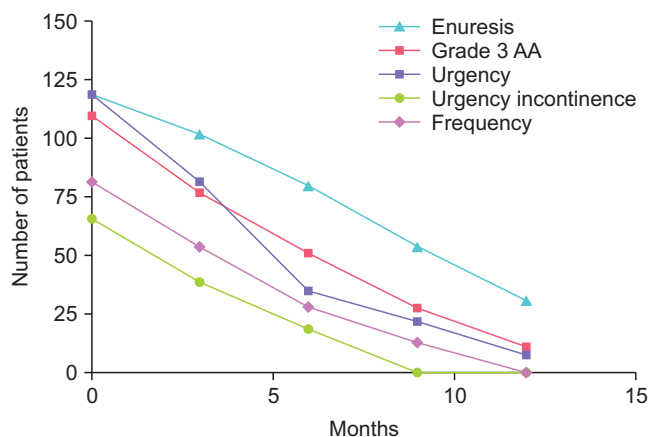
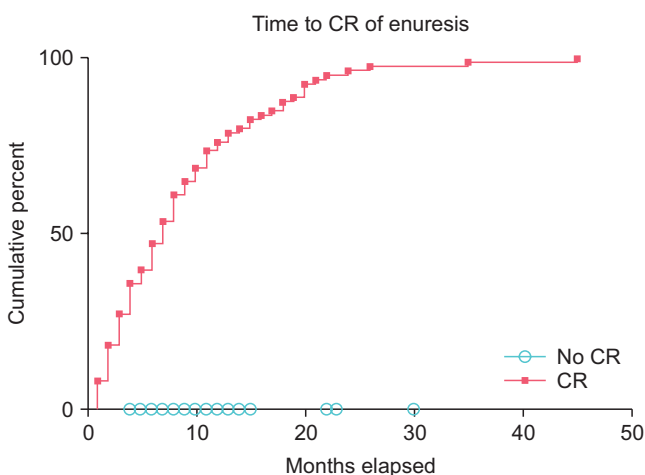
Parameter	Overall values
Mean age (y)	7±2
Male	82 (68.9)
Number of wet nights per week	
≤5	27 (22.7)
≥6	92 (77.3)
ROME III compatible constipation	37 (31.1)
Uroflowmetry	
Bell shape	62 (52.1)
Tower shape	57 (47.9)
Postvoid residual >20 mL	4 (3.4)
Ability to awaken	
Grade 1	0 (0.0)
Grade 2	9 (7.6)
Grade 3	110 (92.4)
Modified DVISS	
Daytime incontinence	66 (55.5)
Voiding frequency (≥8)	52 (43.7)
Incomplete emptying	19 (16.0)
Urgency	119 (100.0)
Holding maneuver	58 (48.7)
Urgency incontinence	49 (41.2)
Voided volume (mL)	
Minimum	45±32
Maximum	168±74
Average	93±53
Median follow-up duration (mo)	15±11

Values are presented as mean±standard deviation or number (%). DVISS, Dysfunctional Voiding and Incontinence Symptom Score.

and 16 (13.4%) patients, respectively, neither of the symptoms were completely resolved and further treatment with additional anticholinergics was warranted. While standard urotherapy was maintained until the resolution of enuresis, treatment of constipation was ceased when there was no positive answer to the ROME III criteria. The median treatment duration for polyethylene glycol was 6 months (range, 3 to 14 months).

Time course changes of AA as well as major LUTD conditions are shown in Fig. 1. The treatment led to significant decreases in urgency, urgency incontinence, frequency, and grade 3 AA. The changing pattern of AA with time was observed to be parallel with these variables. Additionally, enuresis was gradually resolved along with these variables. The number of children showing grade 3 AA markedly decreased from 110 (92.4%) to 57 (47.9%) during 6 months of treatment. The number of children experiencing grade 1 and grade 2 AA at 6 months were 36 (30.3%) and 22 (18.5%), respectively.

To determine whether the change in grade 3 AA bore any relationship to the change in other LUTD symptoms,

**Fig. 1.** Time course of changes in outcome variables following anticholinergic therapy. AA, ability to awaken.**Fig. 2.** Kaplan-Meier estimates regarding time course of cure rates. Those who achieved complete resolution (CR) are described in the shaded squares while those who failed to achieve resolution are shown as blank circles.

we compared the slope by assessing linearity by use of the Runs test (for all variables $p < 0.05$). The estimated equations were $Y = -7.467X + 122.0$, $Y = -8.233X + 103.8$, $Y = -9.400X + 109.6$, $Y = -5.700X + 59.00$, and $Y = -6.833X + 76.40$, corresponding to the prevalence of enuresis, grade 3 AA, urgency, urgency incontinence, and frequency, respectively. A similarly decreasing trend was shared by these variables. As inferred from the changes in distribution, improvement of urgency came first, followed by AA. The alleviation of enuresis came last.

All but 31 patients (26.1%) achieved CR of enuresis during the 45 months of follow-up. Of the 31 patients who failed to achieve CR, 15 patients were followed while waiting for CR and 16 patients were lost to follow-up. The median time for CR was 7 months (range, 2 to 18 months) (Fig. 2). Using multivariate analysis, we attempted to discern the pretreat-

Table 2. Results of the univariate analysis of the effects of pretreatment and treatment variables on rates of complete resolution at 18 months

Variable	CR(+)	CR(-)	p-value
Pretreatment variables (n=119)			
Age			
Higher than 8 years	20	16	0.39
Below 8 years	39	44	
Sex			
Boy	40	42	0.79
Girl	19	18	
Constipation			
Present	17	30	0.02
Absent	42	30	
Treatment variables after 6 months of treatment (n=115)			
Lack of AA improvement			
Yes	43	15	0.001
No	16 ^a	41	
Persistent daytime incontinence			
Yes	27	38	0.02
No	32	18	
Improvement of enuresis (≥50%)			
Yes	33	20	0.02
No	26	36	

CR, complete resolution; AA, ability to awaken.

^a:These 16 patients eventually achieved cure without documented AA. In fact, all of them slept through the night without wetting and waking up and hence AA status could not be assessed (rather than saying that there was no improvement in AA).

ment and 6-month treatment variables that were related to eventual CR at 18 months of treatment. This time limit was determined by the fact the most loss to follow-up occurred within this period.

To identify the clinical characteristics that are unlikely to show CR within 18 months of treatment, univariate analyses included various pretreatment variables such as age (>8 years), sex, and pretreatment constipation and treatment variables at 6 months of treatment such as no improvement in AA, persistent daytime incontinence, and no improvement in enuresis. Of these, pretreatment constipation, no improvement in AA, persistent daytime incontinence, and no improvement in enuresis until 6 months of treatment were found to be significant (Table 2).

Multivariate analyses revealed that persistent daytime incontinence and failure to achieve grade 1 AA until 6 months of treatment were factors for treatment resistance until 18 months of treatment (Table 3).

Table 3. Results of the multivariate analysis on the lack of obtaining complete resolution at 18 months of treatment

Parameter	Odds ratio	Confidence interval	p-value
Pretreatment			
Constipation	0.821	0.19–3.543	0.79
After 6 months of treatment			
Lack of AA improvement	4.613	1.399–15.217	0.01
Persistent daytime incontinence	4.148	1.621–10.612	0.01
Improvement of enuresis (≥50%)	1.42	0.51–3.98	0.21

AA, ability to awaken.

DISCUSSION

The most salient finding was that the successful control of symptoms of LUTD, assumed to be under the control of the bladder, led to improved awakening, which belongs to the realm of the brain. This could support the concept of “bladder-brain dialogue,” suggesting a mutual interaction between the brain and the bladder rather than unidirectional control by the brain. By showing that the treatment which aimed to reduce bladder dysfunction was associated with changes in brain function (AA), we provide evidence to support this concept. Furthermore, we found clear time sequences in which the improvement of AA followed changes in LUTD symptoms with a similar slope in distribution changes. This may imply that the improvement of LUTD is a prerequisite to the acquisition of better AA. A possible explanation is that the reduction of chronic arousal stimuli from the bladder due to the control of daytime symptoms improves sleep deprivation. This in turn facilitates the maturation of the brainstem related to arousal and normalizes the arousal threshold. Consequently, the patient can better sense the bladder filling and can wake up before the enuretic episode. This explanation may fit the gradual time course of AA as well as enuresis as it is related to the maturation of the bladder.

So far, alarms are the only measure to improve arousal. By controlling the bladder, we may be able to address the problem of arousal in a different manner than with alarms. Supporting this, it was reported that normalized bladder control may pave the way for helping with alarms to sense the bladder in an efficient manner [21].

The data confirmed that control of LUTD symptoms was critical in the management of NME. Improvement of enuresis was proportional to that of LUTD symptoms. This was consistent with previous studies underscoring the control of LUTD symptoms for the management of NME [19].

Our data suggest that obtaining information for AA was

useful in predicting the course of treatment for enuresis. Since changes in AA were associated with those in LUTD, improved AA indicated adequate control of LUTD, which is an important prerequisite for the control of enuresis. Furthermore, patients with early acquisition of AA were likely to show better resolution of enuresis than were patients without acquisition of AA. Whether this early resolution of enuresis may simply be attributed to the successful control of LUTD or maturation of brain function adequate for resolution of enuresis requires further study.

Information on AA can be easily gathered by history taking. Thus, we suggest that AA be included in the history taking for patients with enuresis as a possible proxy in assessing baseline severity, predicting response, and evaluating treatment efficacy.

The present study has some limitations. This was a retrospective study and there was no control group to test the roles of the sole management of urotherapy, constipation, anticholinergics, or desmopressin. However, this study intended to observe the clinical response when optimal treatment of NME was given rather than to verify the role of a single treatment modality. Also, 1 month of urotherapy may not be effective in improving enuresis given that long-term urotherapy may be needed to control enuresis [22].

Gathering information on AA from patients, as well as parents, was easy as they showed no difficulty in reporting the information. However, even after improved AA was observed, this might not be improved further in some patients, who experienced regression at the next visit. Thus, one can argue that improvement in AA is an unreliable phenomenon. However, our experience indicated that once achieving improvement in AA, patients easily restore the improved AA following strict control of LUTD as well as constipation. Thus, the state of improvement in AA is certainly better than no improvement, and this is like achieving a developmental milestone, for which the occurrence of a single episode is thought to be meaningful. Thus, we defined improvement as even a single episode of improved response.

CONCLUSIONS

Controlling symptoms of LUTD in the management of NME was crucial not only for the treatment of enuresis but also for allowing patients to obtain better arousal.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Minki Baek, Jung Keun Lee, and Kwanjin Park. Data acquisition: Jung Keun Lee. Statistical analysis: Jung Keun Lee and Hyun Kyu Kim. Data analysis and interpretation: Young Jae Im, Jung Keun Lee, and Kwanjin Park. Drafting of the manuscript: Minki Baek, Jung Keun Lee, and Kwanjin Park. Critical revision of the manuscript: Young Jae Im and Hyun Kyu Kim. Approval of the final manuscript: Kwanjin Park.

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