



Changes in attention variables in those who treated with anticholinergic agents for nonmonosymptomatic enuresis

Gwan Jang , Young Jae Im , Jungyo Suh , Kwanjin Park

Department of Urology, Seoul National University College of Medicine, Seoul, Korea

Purpose: Brain dysfunction related to areas regarding attention and arousal may occur not only in patients with attention-deficit/hyperactivity disorder (ADHD) but also in patients with enuresis and daytime symptoms. This study aimed to investigate changes in computerized comprehensive attention tests (CATs), a psychometric test for ADHD when patients with nonmonosymptomatic enuresis (NME) were treated with anticholinergic agents.

Materials and Methods: Thirty patients with NME featuring overactive bladder were prospectively enrolled. They were treated with 5 mg of solifenacin to control daytime symptoms. Using CATs, patients were evaluated during 12 weeks of treatment. Four subtests of attention (visual and auditory selective attention, sustained attention, and flanker tests) were measured. For each subtest, four domains (omission error, commission error, response time [RT], and standard deviation of RT) were assessed.

Results: Only one domain of the flanker test was in the deficient range at baseline. The presence of urge incontinence affected follow-up results on the sustained attention tests. Treatment with anticholinergic agents did not significantly affect attention variables but changes in several variables were correlated with bladder symptoms and enuresis.

Conclusions: Minimal baseline defects in attention function were seen in patients with NME. Follow-up results for some attention variables were affected by daytime symptoms and enuresis. These results suggest that altered brain function in enuretic patients influences improvement in both attention and bladder function.

Keywords: Central nervous system; Cholinergic antagonists; Nonmonosymptomatic enuresis

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INTRODUCTION

Nocturnal enuresis (NE) is a common condition. Approximately 5% to 10% of 7-year-old children regularly wet their beds. This problem may persist into adolescence and adulthood [1]. A common feature of enuretic children is they are hard-to-awake, deep sleepers, that is, they are not likely to be

awakened by usual stimuli. Recent findings, however, suggest that enuretic children actually show deprived sleep. In fact, they are constantly irritated by various arousal stimuli, such as periodic limb movements during sleep, parasympathetic dominance, constipation, detrusor overactivity, and nocturnal polyuria. Persistence of these stimuli chronically inhibits transition of sleep stages from light to deep sleep. In

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Corresponding Author: Kwanjin Park <https://orcid.org/0000-0002-8926-3047>

Department of Urology, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
TEL: +82-2-2072-0695, FAX: +82-2-742-4665, E-mail: urodori9@snu.ac.kr

response to deprived deep sleep, patients' arousal is affected, consequently changing into the hard-to-awake phenotype to compensate for their deprived sleep. Although this hypothesis has not been fully verified, supporting evidence is steadily increasing [2,3].

Given that that some patients never become enuretic despite the presence of these stimuli [4], peripheral problems are not the sole reason for the hard-to-awake phenomenon. Thus, there should be some intrinsic problems in the central nervous system (CNS) that render patients hard-to-awake. As most enuresis undergoes gradual improvement, immaturity of specific brain regions, which gradually mature later, is likely to play a role in this problem. The most probable areas lie in the pontine micturition center and locus coeruleus, which are located in the brainstem. Thus, we would say immature brainstem function may contribute to the poor arousal leading to the development of enuresis [5,6], especially in the presence of constant peripheral stimuli. Despite the potential relevance, no study has evaluated the role of intrinsic CNS problems with respect to the development of enuresis.

Interestingly, similar areas in the brainstem are also affected in those with attention-deficit/hyperactivity disorder (ADHD) [7]. As expected, ADHD is implicated in both lower urinary tract dysfunction (LUTD) and NE [8]. Neurophysiologic and functional imaging studies have shown common alterations of CNS activity in patients with enuresis as well as ADHD [9-11]. This has also been demonstrated by epidemiologic studies [12,13]. Given this association of enuresis and ADHD, we wondered what would be shown if neurophysiologic tests for ADHD were applied to patients with enuresis. Such study may provide insight to brain immaturity concerning enuresis.

So far, several neurophysiologic and neuropsychological tests have been attempted in enuretic patients. However, the interpretation of such tests may be complicated by two problems. First, most such studies were conducted with all subsets of enuretic patients. Considering that daytime symptoms are more likely to be associated with psychological problems than with enuresis alone, it would be more probable that enuretic patients with daytime symptoms have a higher probability of showing abnormalities in tests than patients with enuresis alone [14-16]. Therefore, abnormal test results are more likely found in nonmonosymptomatic enuresis (NE with LUTD, or NME). The other problem is that only limited data are available on longitudinal changes in neurophysiologic variables because most studies were conducted in a cross-sectional manner. We believe those problems would complicate the assessment of CNS immaturity in the devel-

opment of enuresis. Thus, the primary aim of this study was to know how many neurophysiologic abnormalities might be seen in patients with NME and reveal their nature. By associating clinical course with results of neurophysiologic testing, the secondary aim of this study was to determine whether changes in enuresis or daytime symptoms accompany changes in neurophysiologic tests.

To control daytime symptoms inherent to NME, an anticholinergic agent was administered throughout the study period. Safety concerns, especially effects on attention or memory, could be raised, as previous studies in adults have reported impairment of attention and memory following medication [17-19], although such effects on children have not been reported. Thus, the results of this study could be referred to when considering the central effect of anticholinergic agents on children.

MATERIALS AND METHODS

1. Participants

The present study was a prospective observational study conducted from September 2015 through November 2017. Patients were considered eligible when they showed the following: 1) enuresis of at least three times per week; 2) daytime symptoms such as urgency, frequency, and urge incontinence that constitute overactive bladder (OAB) of NME; 3) history of normal developmental milestones; 4) willingness of patients, as well as parents, to treat enuresis; and 5) capability to swallow pills. Patients were excluded if 1) the age of the child was younger than 4 years or older than 10 years; 2) the child's medical history revealed any kind of developmental, psychological, or neurologic disorder; 3) the child had received any previous treatment related to enuresis; and 4) history suggestive of infrequent (less than three times per day) voiding or overt dysfunctional voiding (frequent urinary tract infection and increased residual urine). The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (approval number: 1511-045-718).

2. Study flow

During the first clinic visit, a history related to enuresis, daytime symptoms, and developmental milestones was thoroughly taken. A physical examination focusing on the genitalia, abdomen, and spine was conducted. Once consent was received from the patients and their caregivers, standard urotherapy education, which included demystification, the anatomy of the urinary tract and voiding physiology, adequate water consumption, timed voiding, and constipa-

tion control, was provided. Parents and patients were asked to revisit 4 weeks later with filling in of the dysfunctional voiding symptom score (DVSS) and 2 days of a voiding diary. To rule out the presence of dysfunctional voiding, uroflowmetry and measurement of postvoid residual urine were done. Only cases with bell or tower-shaped uroflowmetry and normal residual urine were eligible for this study.

When patients were suspected of having OAB, anticholinergic agents were indicated for treatment. The objectives and outline of the study were explained and written informed consent was obtained from participants and their parents. For those who provided consent for this study, a baseline comprehensive attention test (CAT) was done and solifenacin 5 mg was prescribed. Those who showed a constellation of symptoms of constipation were concomitantly treated with polyethylene glycol (0.8 g/kg/d). Follow-up examinations of DVSS, drug log, voiding diary, and CAT were done 6 and 12 weeks later. Adverse events were solicited verbally in each clinic visit. Children and their guardians were asked about not only common adverse effects like dry mouth, facial flushing, and constipation, but also any adverse effects related to the CNS such as behavioral, cognitive, and mood abnormalities following the medication.

Following this study, patients were further treated with solifenacin and desmopressin (0.2 mg/d) as a combination regimen. Time to complete resolution of enuresis was also recorded.

3. Comprehensive attention test

Attention status was evaluated by use of the computerized CAT developed by the Korean Academy of Child

and Adolescent Psychiatry [20,21]. The computerized CAT consisted of six subtests: visual selective attention, auditory selective attention, sustained attention, flanker test, divided attention, and spatial working memory. Since the last two subtests were recommended for children aged 9 to 15 years, these were not applied to most of our population. Thus, they were not included in our analysis. Fig. 1 shows the user interface on the computer screen during the CAT and how to perform the CAT. Briefly, the visual selective attention test (VSAT) assessed the ability to discern a specific shape (e.g., a circle) among other randomly appearing shapes (e.g., star or diamond). The auditory selective attention test (ASAT) measured the ability to respond to the sound of a bell among other randomly appearing sounds (e.g., camera shutter sound, buzzer sound). The sustained attention test (SAT) assessed the ability to maintain a consistent behavioral response during continuous and repetitive activities. Visual stimuli in various shapes were presented every 2 seconds for 10 minutes. Participants were instructed to respond to all shape stimuli except the X shape (Fig. 1). Therefore, the task measured the capacity of participants to inhibit responses to certain stimuli under conditions of sustained attention. The flanker test measured the response to stimuli concentrated on the center while adjacent stimuli (flankers) were ignored. As shown in Fig. 1, patients were requested to choose the direction of an opened square in the middle of five squares, each of which had an opening in the same or opposite direction. This was intended to assess the ability to suppress responses that were inappropriate in a particular context.

For each subtest, we measured four domains: omission errors (OEs), commission errors (CEs), the response time (RT),

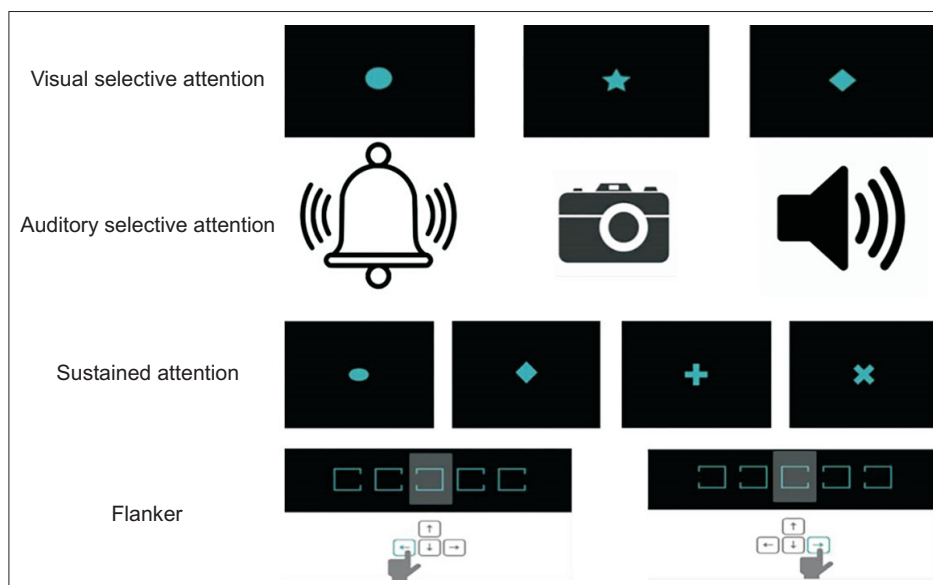


Fig. 1. Schematic drawing explaining the subtests of the comprehensive attention test (CAT) and how to apply the CAT.

Table 1. Pretreatment clinical features of 30 patients

Clinical features	Data
Median age (range)	6 (5–9)
Male	21 (70.0)
Severe enuresis (≥5 times a week)	26 (86.7)
Mean score of DVSS (range)	17.2 (11–25)
DVSS (number of patients reporting more than half of time)	
Urge incontinence (Q1)	7 (23.3)
Constipation (fulfilling both Q3 and Q4)	8 (26.7)
Urgency (Q7)	30 (100.0)
Mean age-adjusted maximal voided volume (range)	67.5 (36–88)
Mean age-adjusted average voided volume (range)	41.6 (21–69)
Shape of uroflowmetry	
Bell	11 (36.7)
Tower	19 (63.3)

Values are presented as number (%) unless otherwise indicated. DVSS, dysfunctional voiding symptom score.

and the standard deviation of the response time (SDRT). OE was defined as the number of missing responses to the target and RT was defined as the mean time to response. They are related to attention processes with lower scores suggesting inattention. CE (number of wrong responses to the target) and SDRT (variability of RT) are thought to be influenced by impulsivity and hyperactivity, with lower scores implying poor control of impulsivity. For each parameter, the result was converted to attention quotient (AQ), assuming that the average was 100 with an SD of 15 in the normal reference population. When a given value was measured to lie below 76, which corresponded to the level of -1.6 SD, patients were diagnosed as having a deficient function for that domain.

4. Statistical analysis

All values are presented as means±SDs unless otherwise specified. Whether the difference was statistically signifi-

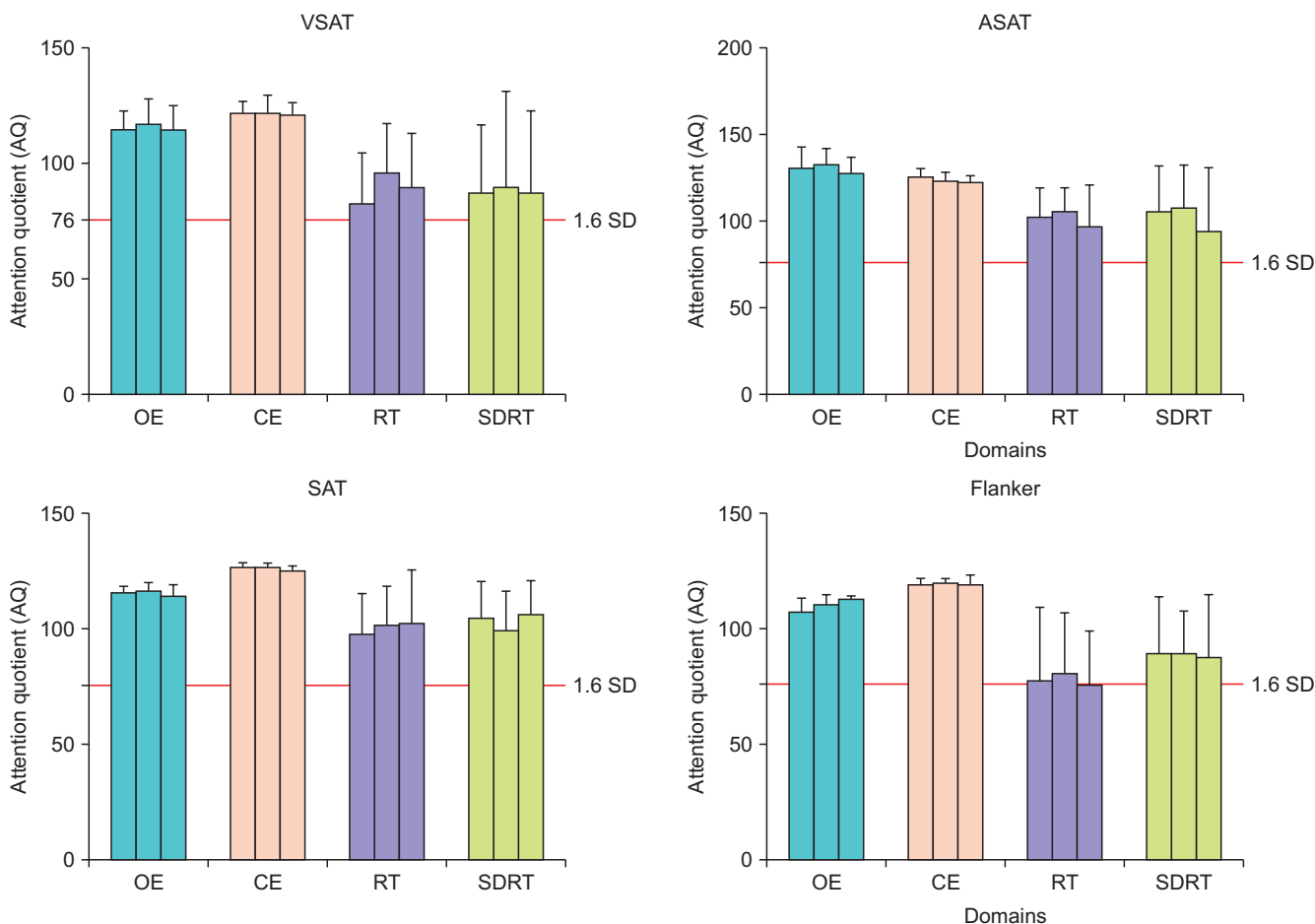


Fig. 2. Overall changes in the comprehensive attention test (CAT) during treatment with solifenacin for 12 weeks. Each domain of a subtest has three columns. These correspond to results at baseline, 6 weeks, and 12 weeks of treatment reading from the left. The red line marks an attention quotient (AQ) of 76, which corresponds to -1.6 SD from 100. Values below this are suggestive of deficiency of attention for a subtest. OE, omission error; CE, commission error; RT, response time; SDRT, standard deviation of response time; VSAT, visual selective attention test; ASAT, auditory selective attention test; SAT, sustained attention test.

cant between the initial and final visits was determined by repeated-measured of analysis of variance (RM-ANOVA). The relationship between the CAT results and changes in daytime symptoms or enuresis was assessed by Spearman's correlation analysis. PASW Statistics version 18.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. A p-value of less than 0.05 was considered statistically significant.

RESULTS

1. Patient and clinical characteristics

Forty patients were originally screened for this study. Of them, three did not meet the inclusion criteria and four declined to participate in the study. Hence, 33 patients were originally enrolled, but 3 patients were lost to follow-up. Thus, 30 patients completed this study. Their clinical characteristics are summarized in Table 1. Their median age was

6 years old. Twenty-one (70.0%) patients were males and 26 (86.7%) showed severe (more than five times a week) enuresis. Although urgency was noted in all patients, daytime incontinence was noted in only 7 patients (23.3%). A history suggestive of constipation on the DVSS (fulfilling both Q3 and Q4) was found in 8 patients (26.7%).

2. Results of treatment of daytime symptoms and enuresis

All patients initially received solifenacin 5 mg for the control of their daytime symptoms. Based on the drug log, the mean drug compliance rate was 92.5%. All prescribed drugs were tolerable. All reported adverse events were mild in degree. Increased constipation was noted in two patients and a transient mild headache was found in one patient. After 12 weeks of treatment, significant improvement in urgency, urge incontinence, and enuresis was noted. Mean total DVSS scores were reduced from 19.5 to 9.4 points from

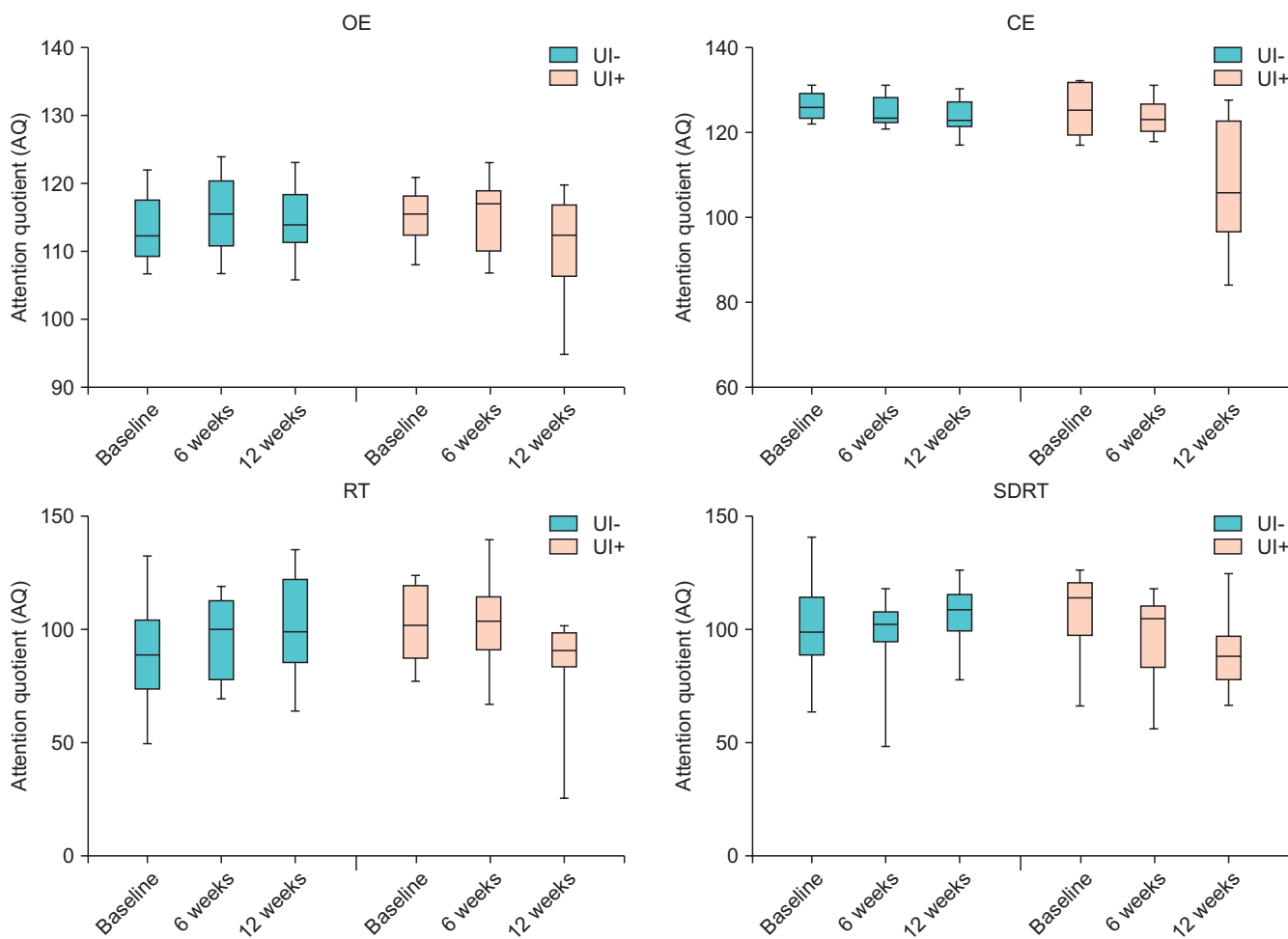


Fig. 3. Comparison of each domain of the sustained attention test with regard to daytime incontinence. Decreasing tendency of attention quotient (AQ) with repetitive tests was seen, especially in patients with daytime incontinence. This was pronounced in commission error (CE) and standard deviation of response time (SDRT), which are related to control of impulsivity. On the other hand, an increasing trend of AQ was seen in those without daytime incontinence. OE, omission error; RT, response time; UI, urinary incontinence.

baseline. In terms of urgency, which was seen in all patients before treatment, complete, partial, and no response was reported in 22 (73.3%), 4 (13.3%), and 4 (13.3%) patients, respectively, at 12 weeks of treatment. Regarding urge incontinence, complete, partial, and no response was seen in 10 (72%), 2 (14%), and 2 (14%) patients, respectively. Enuresis showed a more gradual improvement than daytime symptoms, with complete, partial, and no responses seen in 5 (16.7%), 13 (43.3%), and 12 (40.0%) patients, respectively. At 12 weeks after treatment, patients were further managed with a combination treatment of desmopressin and anticholinergic agents. Eventually, 25 patients (83.3%) achieved complete resolution of enuresis with a median follow-up of 14 months (range, 3–26 months).

3. Overall changes in attention variables

Fig. 2 depicts serial changes in mean tested parameters during 12 weeks of treatment. At baseline, only mean RT in the Flanker test fell within the deficient range of AQ. Twelve weeks of treatment with solifenacin 5 mg did not elicit any significant change in any examined domain ($p > 0.05$ in RM-ANOVA). To evaluate the effect of pretreatment clinical features on overall changes in attention variables, results of subtests were compared between those with and without clinical features such as age (more than 6 years or not), sex, severity of enuresis (more than five times a week or not), presence of daytime incontinence, and constipation. While most subtests did not reveal a significant difference in these features, significant differences in the results of SAT were found when patients showed daytime incontinence. Patients with daytime incontinence showed a declining tendency of AQ with repetitive tests in all domains of sustained attention ($p < 0.05$, two-way RM-ANOVA, Fig. 3).

4. Correlation analysis

To assess the relationship of attention variables with variables related to enuresis, correlation analysis was performed (Table 2). Changes in DVSS and percentage increase in maximal voided volume between baseline and the final visit (V3-V1) were measured as a surrogate for the control of daytime symptoms. For enuresis, time to complete resolution was also evaluated (Table 2). CEs and SDRTs in domains of the VSAT and ASAT were significantly correlated with these aforementioned variables. Thus, improvement of some variables on the CAT was correlated with a reduction of daytime symptoms, increase in bladder volume, and early resolution of enuresis.

Table 2. Correlation analysis between variables related to enuresis and domains related to enuresis

Spearman's Rho	Age	DVSS changes	% MVV increase	Time to CR
VSAT (V3-V1)				
OE	0.053	-0.006	-0.012	-0.046
CE	0.235	-0.421 ^a	0.582 ^a	-0.459
RT	-0.342	0.222	-0.206	-0.036
SDRT	-0.326	0.254	0.223	-0.163
ASAT (V3-V1)				
OE	0.233	0.034	0.226	-0.279
CE	0.470 ^a	-0.450 ^a	0.127	-0.516 ^a
RT	-0.180	-0.280	-0.146	0.259
SDRT	0.008	-0.559 ^a	0.262	0.081
SAT (V3-V1)				
OE	-0.063	0.317	-0.114	0.349
CE	0.160	-0.196	0.304	-0.169
RT	-0.076	-0.280	-0.140	0.031
SDRT	-0.048	-0.324	-0.075	-0.396
Flanker (V3-V1)				
OE	-0.159	0.334	-0.156	-0.084
CE	-0.068	-0.325	0.280	-0.331
RT	0.047	0.000	0.008	-0.366
SDRT	0.122	-0.009	0.194	-0.369

DVSS, dysfunctional voiding symptom score; MVV, maximal voided volume; CR, complete resolution; VSAT, visual selective attention test; OE, omission error; CE, commission error; RT, response time; SDRT, standard deviation of response time; ASAT, auditory selection attention test; SAT: sustained attention test.

^a:Statistical significance ($p < 0.05$).

DISCUSSION

The major findings of our study were as follows: 1) no deficiency in the CAT was found except in the case of RT on the flanker test; 2) patients with daytime incontinence at baseline behaved differently from those without such on the SAT; 3) treatment with anticholinergic agents did not significantly alter the results of the CAT; and 4) several domains, especially those related to impulsivity (CE and SDRT), were correlated with control of daytime symptoms and enuresis.

Only a few studies have applied neurophysiologic or neuropsychological testing to patients with NE. Our study adds more knowledge to the current database regarding patients with NME. Most studies have tried to evaluate the effect of enuresis on patients with ADHD. Elia et al. [22] reported that patients with ADHD show a higher likelihood of inattentive symptoms than those who do not have ADHD when they have enuresis. Another study conducted on ADHD children reported that patients with enuresis show shorter reaction time in inhibitory control, working memory, and auditory sustained attention [23]. Thus, the presence of

enuresis is the main cause of differences in neuropsychiatric tests in patients with ADHD. Only one group has tried to apply neuropsychological testing to those with monosymptomatic enuresis (ME) [24,25] and found the dominance of inattentive symptoms of ADHD in patients with ME, consistent with the previous study [22]. Our study was distinctive in that it was conducted in another kind of enuretic patient population (NME) by applying a novel neurophysiologic test rather than a neuropsychological one. Although NME has not been explored as much as ME, it is even more important than ME in terms of prevalence, severity, and tendency to refractoriness [26,27]. At baseline, all variables except RT on the flanker test showed normal ranges. The flanker test is a test to determine the ability to maintain attention in the presence of disturbing stimuli [28]. A proper response to the test is dependent on the activity of the anterior cingulate cortex (ACC), whose activation leads to suppression of bladder activity. Hence, isolated deficiency in RT on the flanker test may indicate immaturity of the ACC, which could be found in patients with NME. However, this immaturity was not severe enough to affect other variables in the flanker test or other domains of the CAT. Furthermore, there was no correlation between RT on the flanker test and clinical courses of enuresis or daytime symptoms. Therefore, the presence of NME does not appear to harbor severe abnormality in the brainstem. This non-severe brain dysfunction might be the background for the natural improvement of enuresis and maturation of brain function with age.

Although minimally significant baseline deficiency was noted in patients with NME, those with urge incontinence at baseline tended to get worse scores in sustained attention compared with those without urge incontinence. This was seen only in CE and SDRT, which are related to impulsivity. This was interesting because the abnormality found in those with urge incontinence was not related to other attention variables or outcomes of daytime symptoms and enuresis, so this may reflect the impatient nature of those with urge incontinence as opposed to those without when they are exposed to repetitive tests. However, this finding may be explained by the fact that ADHD is more common in those with daytime wetting. In addition, deficient sustained attention is a cardinal problem in ADHD [13,23,25]. However, the lack of association with clinical outcomes supports the claim that the brain regions related to ADHD and enuresis are near each other but not identical.

Despite pretreatment abnormalities in several attention variables, the treatment did not elicit any changes in attention variables during 12 weeks of treatment. This supports that anticholinergic treatment has minimal harmful effects

on attention variables in those who were treated by solifenacin. Although we could not say this might be applied to other anticholinergic agents, some typical adverse effects found in children following treatment with anticholinergic agents were seen in much fewer numbers than in adults in the case of solifenacin [29,30].

More reduction of DVSS indicating greater improvement of daytime symptoms was correlated with increasing AQs of CEs in the domain of visual selective attention or auditory selective attention. A similar relationship was also found between these above-mentioned attention variables and early resolution of enuresis. Despite the limitation of correlation analysis, which does not prove a cause and effect relationship, our data support the presence of brain-bladder dialogue and underline that active treatment of the bladder may improve bladder function as well.

To summarize our results, we suggest that, in terms of CAT, patients with NME showed a mild baseline abnormality in attention and this improved in accordance with the control of bladder. Thus, control of the bladder may provide a chance to improve attention function, thus supporting bladder-brain dialogue. Applying solifenacin to control the bladder did not do any harm in CAT variables.

An important limitation of this study was the lack of healthy control patients. In addition, the number of participants in the NE group was limited. Furthermore, we could not provide information on the causal link between these conditions because of the cross-sectional nature of this study.

CONCLUSIONS

In conclusion, patients with NME showed marginal abnormality in overall neurophysiologic tests. However, an increasing number of abnormalities was seen when daytime urinary incontinence was present. While treatment with anticholinergic agents elicited no significant abnormality, changes in parameters related to impulsivity were related to the course of enuresis and daytime symptoms. These findings suggest that there is a connection between the bladder and the brain, and it may be related to disease severity.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Data management and analysis, manuscript writing: Gwan Jang. Protocol/project development, data collection: Young Jae Im, Jungyo Suh, and Kwanjin Park. Manuscript editing: Kwanjin Park.

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