

# Clinical usefulness of the attention-deficit hyperactivity disorder rating scale-IV in the treatment of enuretic children undiagnosed with developmental disorders

Masaki Fuyama\*<sup>1</sup>, Hirokazu Ikeda<sup>1,2</sup>, Chisato Oyake<sup>2</sup>,  
Yuta Onuki<sup>3</sup> and Tsuneki Watanabe<sup>2</sup>

Received: 10 June 2020 / Accepted: 9 September 2020

## Abstract

To determine the association between attention-deficit hyperactivity disorder (ADHD) and nocturnal enuresis (NE) and its relation to the effectiveness of NE treatment in children undiagnosed with developmental disorders. A total of 154 children with NE (112 males and 42 females) were included in this study, aged  $\geq 5$ – $< 15$  years, presenting at the Department of Pediatrics, Showa University Fujigaoka Hospital, between January 2016 and June 2017. None of the participants was diagnosed with developmental disorders. We retrospectively evaluated Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores, Dysfunctional Voiding Symptom Score (DVSS), NE clinical characteristics, and efficacy of NE treatment. The mean age was  $8.0 \pm 2.0$  years (standard deviation). Sixty-seven (40.3%) patients presented with daytime incontinence (DI). The mean total ADHD-RS and DVSS scores were  $7.7 \pm 8.0$  and  $6.6 \pm 4.3$ , respectively, and they were significantly correlated ( $p = 0.049$ ). ADHD-RS scores were significantly higher in patients with DI than in those without DI ( $p = 0.0006$ ). ADHD-RS scores and large-volume DI (a DVSS subscale item) were significantly correlated. Six months after treatment initiation, patients with  $< 50\%$  improvement (nonresponder) in NE had significantly higher total ADHD-RS scores than those with  $\geq 50\%$  improvement (responder) ( $p = 0.007$ ). Even in patients not diagnosed with developmental disorders, ADHD characteristics may influence the clinical course of NE. Evaluation of ADHD characteristics using a screening tool such as the ADHD-RS is important in the NE treatment.

**Key words**: enuresis, urinary incontinence, attention-deficit hyperactivity disorder, lower urinary tract symptoms

## Introduction

Nocturnal enuresis (NE) results from various factors, such as polyuria, abnormal urine storage mechanisms, and sleeping disorders<sup>1</sup>; however, recent findings have established a relationship between NE and developmental disorders<sup>1-5</sup>.

Attention-deficit hyperactivity disorder (ADHD)

is a developmental disorder characterized by hyperactivity, impulsiveness, and inattentiveness.

Previously, a correlation between NE and ADHD was found (odds ratio, 2.88; 95% confidence interval; 1.26–6.57)<sup>6</sup>, and children with NE and ADHD are more likely to complain of daytime incontinence (DI)<sup>7</sup>. Compliance with lifestyle modifications for NE and DI can be difficult in patients with ADHD, and treatment for ADHD may be needed prior to NE and DI treatments. Therefore, understanding and considering ADHD characteristics in therapeutic and educational NE and DI treatments are clinically important. However, identifying ADHD characteristics during NE and DI treatments is not always easy.

The ADHD Rating Scale-IV (ADHD-RS-IV) is one of the most widely utilized screening measures for ADHD characteristics<sup>8</sup>. Several studies have

\* Corresponding author

✉ Masaki Fuyama  
ogr.7101@hotmail.co.jp

<sup>1</sup> Department of Pediatrics, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba-ku, Yokohama-shi, Kanagawa 227-8501, Japan.

<sup>2</sup> Children's Center, Showa University Northern Yokohama Hospital.

<sup>3</sup> Division of Nephrology, Saitama Children's Medical Center.

reported the relationship between ADHD and NE and DI<sup>9,10</sup>. However, the correlation between ADHD-RS scores and NE and DI in children not diagnosed with developmental disorders has not been fully explored. Therefore, we assessed the ADHD-RS scores, Dysfunctional Voiding Symptom Score (DVSS)<sup>11</sup>, which is an index of lower urinary tract symptoms (LUTS), NE clinical characteristics, and responsiveness to NE treatment in children with NE not diagnosed with developmental disorders.

## Materials and methods

### Target Population

The potential participants were 176 patients, aged  $\geq 5$ – $<15$  years, who visited the Department of Pediatrics, Showa University Fujigaoka Hospital, Japan, between January 2016 and June 2017, presenting with NE. Eighteen patients diagnosed with developmental disabilities by a psychiatrist in other hospitals and four patients with concomitant underlying diseases (meningocele,  $n=1$ ; urethral strictures,  $n=2$ ; bladder diverticulum,  $n=1$ ) were excluded. A final total of 154 patients were included.

### Methods

We conducted a retrospective study to determine the correlations among ADHD-RS scores, DVSS, NE clinical characteristics, and efficacy of NE treatment using the patients' medical records. At the first visit, the patients' statuses were recorded by their families

for the last month on the ADHD-RS and DVSS questionnaires.

ADHD-RS is a tool used for ADHD screening, diagnosis, and treatment evaluation, consisting of 18 questions that measure hyperactivity, impulsiveness, and inattentiveness<sup>8</sup>. Each question assesses the frequency of behavior on a scale of 0–3 (0, never or rarely; 1, sometimes; 2, often; 3, very often); the higher the score, the greater the symptom impairment<sup>8</sup>.

The DVSS questionnaire<sup>11</sup> was developed by the Hospital for Sick Children, affiliated with the University of Toronto, to evaluate LUTS, such as DI, volume of urine leakage, and urinary frequency in children<sup>11</sup>. It is comprised of seven LUTS and two bowel symptoms questions scored on a scale of 0–3 (0, almost never; 1, less than half the time; 2, about half the time; and 3, almost every time).

In this study, the Japanese versions of ADHD-RS (Figure 1) and DVSS (Figure 2) were utilized.

The patients and their parents were informed about NE treatments including pharmacotherapy (desmopressin, orally disintegrating tablets) and alarm therapy after initial 4–12-week behavioral therapies, such as water restriction, to choose one of them. In the case of choosing pharmacotherapy, 120  $\mu\text{g}$  of desmopressin was given daily for 2–4 weeks; partial responders were maintained on the same dose, whereas an increased dose of 240  $\mu\text{g}$  daily was administered to the nonresponders, based on the

### ADHD Rating Scale (ADHD-RS)

1. Fails to give close attention to details or makes careless mistakes in schoolwork
2. Fidgets with hands or feet or squirms in seat
3. Has difficulty sustaining attention on tasks or play activities
4. Leaves seat in a classroom or in other situations when expected to remain seated
5. Does not seem to listen when spoken to directly
6. Runs about or climbs excessively in inappropriate situations.
7. Does not follow through on instructions and fails to finish work
8. Has difficulty playing or engaging in leisure activities quietly
9. Has difficulty organizing tasks and activities
10. Is "on the go" or acts as if "driven by a motor"
11. Avoids tasks (e.g., schoolwork, homework) that require sustained mental effort
12. Talks excessively
13. Loses things necessary for tasks or activities
14. Blurts out answers before questions have been completed
15. Is easily distracted
16. Has difficulty awaiting turn
17. Is forgetful in daily activities
18. Interrupts or intrudes on others

Never or rarely	0
Sometimes	1
Often	2
Very often	3

Fig. 1. Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV).

### Dysfunctional Voiding Symptom Score (DVSS)

1. I have had wet clothes or wet underwear during the day
  2. When I wet myself, my underwear is soaked
  3. I miss having a bowel movement every day
  4. I have to push for my bowel movements to come out
  5. I only go to the bathroom one or two times each day
  6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance"
  7. When I have to pee, I cannot wait
  8. I have to push to pee
  9. When I pee it hurts
  10. Parents to answer:  
Has your child experienced something stressful like the example below?  
New baby, Abuse (sexual/physical), New home, Home problems (divorce/death), New school,  
Special events (birthday), Accident/injury, School problems, Others
- |                         |   |
|-------------------------|---|
| Almost never            | 0 |
| Less than half the time | 1 |
| About half the time     | 2 |
| Almost every time       | 3 |

Fig. 2. Dysfunctional Voiding Symptom Score (DVSS).

number of wet nights. Initial nonresponders who achieved a complete response (CR) for  $\geq 4$  weeks during the treatment at the higher dose had their dose reduced to 120  $\mu\text{g}$ , whereas in patients with a maintained CR with  $\geq 4$  additional weeks at the 120  $\mu\text{g}$  dose, the dose was further lowered to 120  $\mu\text{g}$  on alternate days for 8 weeks.

#### Definitions

NE: Nocturnal enuresis, one or more episodes of nighttime incontinence per month lasting for at least 3 months.

DI: Daytime incontinence for at least 1 day per month lasting for at least 3 months.

Constipation: Fewer than three bowel movements (defecation) per week.

CR: Complete response, urine leakage completely resolving or decreasing to less than once a month.

PR: Partial response, the number of days of urine leakage decreased by  $\geq 50\%$ .

NR: Nonresponse, the number of days of urine leakage decreased by  $< 50\%$ .

#### Ethical Standards

This study was approved by the Ethics Committee of Showa University Fujigaoka Hospital (permit number: F2019C67) and was conducted following the principles of the Declaration of Helsinki 1964. Informed consent was obtained from all the parents prior to enrolling their children.

#### Statistical Analyses

Data analysis was conducted using JMP<sup>®</sup> Pro version 10.0 (SAS Institute Inc., Cary, NC, USA).

Numerical variables (age, ADHD-RS score, and DVSS score) were presented as means and standard deviations and were compared using Wilcoxon's rank-sum test. Categorical variables (sex, DI, PR, and NR) were presented as counts and percentages and compared using the chi-square test.  $p < 0.05$  value was considered significant.

### Results

#### Patient Characteristics

The study population included 154 patients (112 [72.3%] boys and 42 [27.3%] girls; mean age  $\pm$  standard deviation 7.97  $\pm$  1.96 years). Sixty-two patients (40.3%) complained of DI, 11 (7.1%) of constipation, and 17 (11.0%) of fecal incontinence. The average wet nights per week at the first visit was 5.16  $\pm$  2.29, and the median follow-up duration was 12 months.

#### DVSS Total and Subscale Scores

The mean total DVSS was 6.63  $\pm$  4.24. There were no significant sex differences in total DVSS ( $p = 0.693$ ); however, older age was associated with significantly lower total DVSS ( $p < 0.0001$ ). There was no significant relationship between total DVSS and average wet nights per week at the first visit ( $p = 0.118$ ).

Means and standard deviations for the DVSS subscale scores were as follows: incontinence during the day, 0.97  $\pm$  1.26; large-volume DI, 0.98  $\pm$  1.25; low-frequency urination, 0.82  $\pm$  0.85; urinary urgency, 1.55  $\pm$  1.06; urination posture, 1.10  $\pm$  1.12; painful urination, 0.05  $\pm$  0.21; dysuria, 0.16  $\pm$  0.55; the interval between bowel movements, 0.34  $\pm$  0.65; dyschezia, 0.64  $\pm$  0.90.

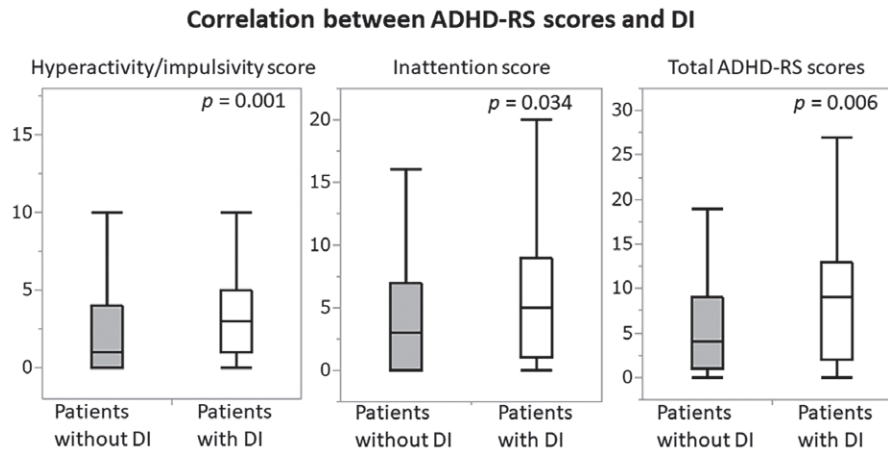


Fig. 3. Correlation between Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores and DI.

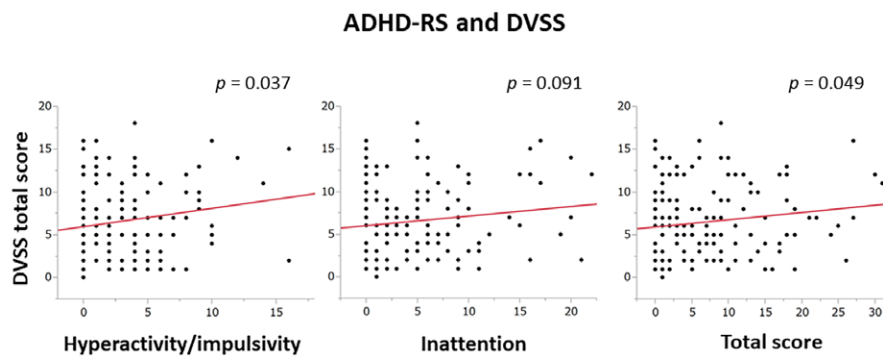


Fig. 4. Correlation between Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores and Dysfunctional Voiding Symptom Score (DVSS).

#### ADHD-RS Scores

The means and standard deviations for total ADHD-RS scores were  $7.67 \pm 8.00$  (hyperactivity and impulsivity scores:  $2.82 \pm 3.34$ ; inattention scores:  $4.84 \pm 5.16$ ). No significant sex differences were observed ( $p = 0.734$ ). Hyperactivity and impulsivity scores significantly decreased with age ( $p = 0.018$ ); however, inattention and total ADHD-RS scores were not significantly correlated with age ( $p = 0.678$  and  $0.471$ , resp.). Patients with DI had significantly higher total ADHD-RS scores than those without DI ( $p = 0.006$ ) (Figure 3). There was no significant correlation between the average wet nights per week at the first visit and total ADHD-RS scores ( $p = 0.535$ ).

#### Correlation Between DVSS and ADHD-RS Scores

There were significant positive correlations between the total DVSS and ADHD-RS hyperactivity and impulsivity subscale scores ( $p = 0.037$ ) and total ADHD-RS score ( $p = 0.049$ ) (Figure 4). Table 1 demonstrates the correlations between ADHD-RS and DVSS individual subscale scores. ADHD-

RS hyperactivity and impulsiveness scores were significantly correlated with incontinence during the day ( $p = 0.0096$ ), large-volume DI ( $p = 0.0078$ ), low-frequency urination (1-2 times per day) ( $p = 0.0484$ ), and dysuria ( $p = 0.0233$ ). Total ADHD-RS and ADHD-RS inattentiveness scores were related only to large-volume DI ( $p = 0.0149$ ;  $p = 0.0425$ , resp.) (Figure 5).

#### Correlation Between the Efficacy of NE Treatment and ADHD-RS Scores

After initiating treatment, 110 out of 154 patients were followed up for  $>6$  months; the treatment effect at 6 months was CR in 15 (13.6%), PR in 59 (53.6%), and NR in 36 (32.7%) patients. There were no significant sex differences. The mean time from treatment initiation to CR in children with NE was  $19.4 \pm 15.0$  months, and there were no medication side-effects.

A comparison of ADHD-RS scores between the response (PR and CR) and nonresponse (NR) groups was carried out to examine the relationship

Table 1. The relationship between Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) and Dysfunctional Voiding Symptom Score (DVSS) ( $p$  value)

	ADHD-RS		
	Hyperactivity and impulsivity	Inattention	Total score
Total DVSS	0.0371	0.0914	0.0486
DVSS subscales			
Number of DI days	0.0096	0.1795	0.0505
Large-volume DI	0.0078	0.0425	0.0149
Low-frequency urination	0.0484	0.5306	0.2176
Urinary urgency	0.2418	0.3595	0.2773
Urination posture	0.1399	0.2358	0.1646
Painful urination	0.1561	0.0501	0.0619
Dysuria	0.0233	0.1334	0.0540
Intervals between bowel movements	0.7512	0.7347	0.9310
Dyschezia	0.8058	0.7585	0.7620

DI : daytime incontinence.

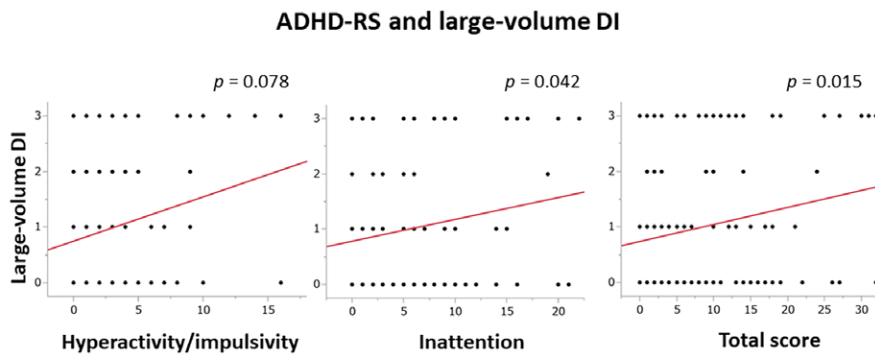


Fig. 5. Correlations between Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores and large-volume daytime incontinence (DVSS subscale) scores.

**Correlations between efficacy of NE treatment and ADHD-RS scores**

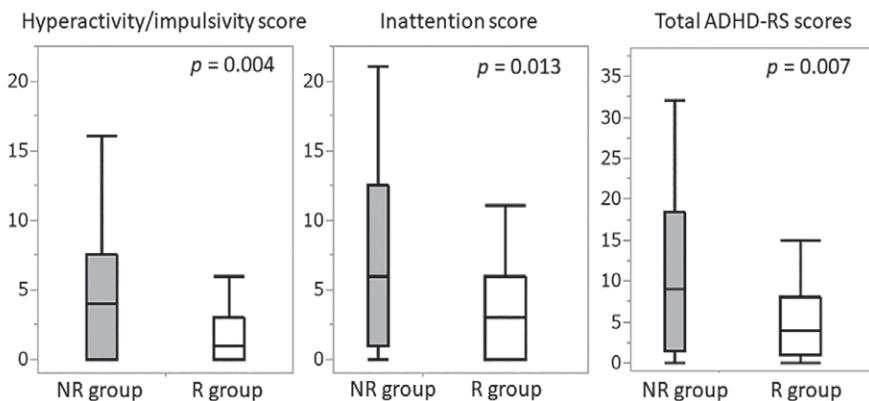


Fig. 6. Correlations between the efficacy of nocturnal enuresis (NE) treatment and Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores at the first visit.

NR group : nonresponse group, NE decreased by < 50% from the initial visit.  
 R group : response group (PR or CR), NE decreased by ≥ 50% from the initial visit.



between the efficacy of NE treatment and ADHD-RS scores. It indicated that all ADHD-RS scores at the first visit were higher in the nonresponse group than those in the response group (Figure 6).

## Discussion

NE prevalence differs according to the region and studies: 15%–20% at the age of 5 years; 5%–10% at 7 years; 5% at 10 years; 1%–3% at 15 years<sup>1,12–14</sup>. About 15%–40% of children with NE had LUTS-related complications<sup>15,16</sup>; however, the reported incidence of these complications is as high as 50%–80%<sup>17</sup>.

ADHD is a developmental disorder and characterized by hyperactive, impulsive, and inattentive<sup>18</sup> behaviors, affecting 3%–5% of children<sup>19</sup>. The symptoms are 3–4 times more common in boys than in girls, and inattentiveness becomes increasingly evident with age. Furthermore, NE and DI are 2.7 and 4.5 times more common, respectively, in children with ADHD than in healthy children.

DVSS were significantly higher for children with ADHD than for healthy children<sup>20–22</sup>; therefore, assessing ADHD characteristics and LUTS is highly important in children with NE. In this study, there is a significant correlation between higher ADHD-RS scores and higher DVSS even in children with NE not diagnosed with ADHD, similar to previous findings for children with ADHD<sup>20–22</sup>.

High ADHD-RS scores only indicate the presence of hyperactivity and inattention characteristics. However, to diagnose ADHD, clear evidence that these symptoms interfere with or reduce the quality of social functioning is required<sup>23</sup>. Although children with high ADHD-RS scores may exhibit similar characteristics to those in children with ADHD, the diagnosis of ADHD is only established in some children with high ADHD-RS scores. Further studies are warranted to assess the differences between NE characteristics with ADHD and NE characteristics with high ADHD-RS scores only.

Yang *et al.* analyzed DVSS subscale scores of NE children with and without ADHD. The ADHD group had significantly higher urinary urgency (cannot wait) and low-frequency urination (urinating 1–2 times/day) scores than the non-ADHD group<sup>20</sup>. In contrast, in this study, ADHD-RS hyperactivity and impulsivity scores were significantly correlated with DVSS subscale scores, including incontinence during the day, large-volume DI, and low-frequency urination (1–2 times daily), whereas urinary urgency was not correlated with

total ADHD-RS, hyperactivity, impulsivity, and inattention scores. The pathologies for NE and DI in ADHD include impaired urinary signal sensing from the bladder owing to decreased frontal-striatal responses, voiding urgency due to overconcentration caused by dopaminergic nervous system dysfunction, and inadequate capacity to respond to the timing of voiding because of behavioral factors such as hyperactivity and inattention<sup>7,21</sup>. In this study, more pronounced ADHD hyperactivity and impulsivity symptoms were related to higher volume for each urinary incontinence episode and lower urination frequency. Therefore, urinary incontinence in these children was associated with poor awareness of the need to void and delayed timing of voiding, rather than urge incontinence due to bladder overactivity. The outcomes of this study are different from those of previous studies revealing that children with ADHD experience a high urgency. However, urgency assessment in children is challenging; thus, this should be thoroughly investigated in the future.

ADHD treatment may improve NE and DI, and evaluating ADHD characteristics in children with NE and DI is of critical importance<sup>4</sup>. However, it is challenging for physicians, other than child psychiatrists, to objectively assess ADHD characteristics, even if ADHD is suspected during NE and DI treatments. Particularly, since hyperactivity and impulsivity become less noticeable and inattention becomes prevalent with age, evaluating inattention within the timeframe of examinations is of a great challenge. Hyperactivity, impulsivity, and inattention can be easily evaluated using the ADHD-RS, and the collected information may be beneficial for applying lifestyle modifications. Besides, this tool is a useful index enabling families to request recommendations for medical examinations from specialists. ADHD-RS was originally developed to screen ADHD and evaluate therapeutic effectiveness; however, ADHD cannot be solely diagnosed using this tool; thus assessments conducted by a child psychiatrist are required. Once ADHD has been diagnosed by a psychiatrist, pharmacotherapy and psychosocial treatments will make lifestyle guidance for NE and DI more effective. Additionally, assessment of ADHD characteristics is useful in tailoring an NE treatment based on the child's developmental characteristics. In children with ADHD characteristics, cognition of voiding frequency as a visual event and setting attainable goals are critical. If a child cannot systematically go to the toilet, using methods such as periodic voiding alarms could be considered.

Moreover, improving a child's self-esteem and promoting the continuation of NE and DI treatments are highly important.

The presence of ADHD complications in children with NE does not influence the therapeutic effects of pharmacotherapy, such as the use of desmopressin<sup>20,22</sup>. However, in this study, children with NR had significantly higher ADHD-RS scores than those with PR or CR 6 months after treatment initiation. Although compliance with lifestyle guidance and pharmacotherapy might have influenced the study's results, these factors were not evaluated. Therefore, further investigation is required.

This study had some limitations as follows. Ideally, the ADHD-RS should be administered in two settings: at school and at home; however, the tool was employed only in the home setting. Therefore, families may have underestimated or overestimated the children's restlessness and inattention. Sex, age, and racial differences in ADHD-RS scores have been considered. Generally, inattentiveness, rather than hyperactivity or impulsivity, is more prevalent in older children and girls, presenting statistical limitations for the analyses. In this study, DVSS and ADHD-RS scores were evaluated only at the first visit. Thus, consecutive assessments of the scores and long-term evaluation of the associations between DVSS and ADHD-RS scores and therapeutic effects are still needed. Autism spectrum disorder may have an effect on NE and DI; however, herein, this aspect was not considered. This study was conducted at a university hospital and included several children who were referred because of poor responses to standard therapy, resulting in patients' background characteristics bias.

This study identified a correlation between DVSS and ADHD-RS scores and demonstrated that ADHD-RS scores were higher in children whose NE decreased by <50% than in children whose NE decreased by ≥50%. Therefore, in the clinical management of NE, assessing the developmental characteristics and LUTS is essential for children not diagnosed with developmental disorders. Using screening tools, such as ADHD-RS, facilitates the evaluation of developmental characteristics, even for general pediatricians who are not specialists in psychiatry, leading to a more effective NE treatment.

#### Conflict of interest disclosure

The authors declare no conflicts of interest associated with this manuscript.

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