Original article

Lower urinary tract dysfunction in children with attention deficit hyperactivity disorders

Disfunción del tracto urinario inferior en niños con trastorno por déficit de atención e hiperactividad

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Abstract

Goal: the aim of this work was to identify the various types of lower urinary tract dysfunctions (LUTD among children with Attention Deficit Hyperactivity Disorders (ADHD) and their responses to treatments.
Methods: this prospective work had been conducted on participants aged 6 -18 years old, who fulfilled criteria for ADHD with any type of LUTD and only naive patients who had no previous urological treatment. All patients were subjected to the standard psychiatric treatment in form of Atomoxetine and/or methylphenidate. The patients were re-evaluated at 1,3,6 months to assess improvement of daytime symptoms and nocturnal enuresis (NE).
Results: in our 60 patients, there was no significant different between recurrence rate of NE and type of ADHD and NE. There was no significant different between type of ADHD according to response of enuresis treatment. Regarding response of treatment of daytime symptoms, 14 (77.7 %) patients showed full response, while 4 (22.2 %) patients did not show response. In patients with NE, 28 (66.7 %) patients showed full response, 8 (19.0 %) patients showed intermediate response, and 6 (14.3 %) patients did not show response. While in patients with non- monosymptomatic NE, 14 (77.8 %) Patients with showed full response, while 4(22.2 %) did not show response.
Conclusions: a combination therapy of desmopressin and imipramine is efficient treatment of monosymptomatic NE in ADHD children, while anticholinergic drugs plus desmopressin are effective in non-monosymptomtic NE.
Limitations: number of cases is small and further multicenter studies are needed to confirm our conclusion.
Originality: this manuscript describes an original work.

Keywords:
Lower Urinary Tract Dysfunction, Attention Deficit Hyperactivity Disorders, Nocturnal Enuresis

Citation: Elgohary M., El Gamal O., Abdel-Hakeem M., Elmaadawy M., Nagla S. *Lower urinary tract dysfunction in children with attention deficit hyperactivity disorders. Rev Mex Urol. 2024;85(4)* 1-11

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Accepted: August 13, 2025.
Received: November 9, 2024.

Resumen

Objetivo: el objetivo de este trabajo fue identificar los diversos tipos de disfunciones del tracto urinario inferior (DUIT) en niños con Trastorno por Déficit de Atención e Hiperactividad (TDAH) y su respuesta al tratamiento.
Métodos: este estudio prospectivo se realizó con participantes de 6 a 18 años que cumplían los criterios de TDAH con cualquier tipo de DUIT, y solo con pacientes sin tratamiento urológico previo. Todos los pacientes recibieron el tratamiento psiquiátrico estándar con atomoxetina y/o metilfenidato. Los pacientes fueron reevaluados a los 1, 3 y 6 meses para evaluar la mejoría de los síntomas diurnos y la enuresis nocturna (EN).
Resultados: en nuestros 60 pacientes, no se observaron diferencias significativas entre la tasa de recurrencia de la EN y el tipo de TDAH. No se observaron diferencias significativas entre el tipo de TDAH y la respuesta al tratamiento de la enuresis. En cuanto a la respuesta al tratamiento de los síntomas diurnos, 14 (77,7 %) pacientes mostraron una respuesta completa, mientras que 4 (22,2 %) mostraron una respuesta completa. Los pacientes no mostraron respuesta. En pacientes con EN, 28 (66,7 %) mostraron respuesta completa, 8 (19,0 %) mostraron respuesta intermedia y 6 (14,3 %) no mostraron respuesta. En pacientes con EN no monosintomática, 14 (77,8 %) mostraron respuesta completa, mientras que 4 (22,2 %) no la mostraron.
Conclusiones: la terapia combinada de desmopresina e imipramina es eficaz para el tratamiento de la EN monosintomática en niños con TDAH, mientras que los fármacos anticolinérgicos más desmopresina son eficaces para la EN no monosintomática.
Limitaciones: el número de casos es pequeño y se necesitan más estudios multicéntricos para confirmar nuestra conclusión.
Originalidad: este manuscrito describe un trabajo original.

Palabras clave:
Disfunción del tracto urinario inferior,
Trastornos por déficit de atención e hiperactividad,
Enuresis nocturna

Background

Attention Deficit Hyperactivity Disorder (ADHD) is among the most prevalent neurodevelopmental diseases in children. Children with ADHD might experience difficulties in sustaining focus, regulating impulsive behaviours, or exhibit hyperactivity.[1] ADHD manifests in three distinct forms, contingent upon the predominant symptoms shown by the person. The mostly inattentive presentation is characterised by difficulty in organising or completing tasks, maintaining attention to details, and adhering to directions or discussions. The individual is prone to distraction or tends to forget aspects of regular tasks.[2] A kid with ADHD is associated with a heightened probability of disruptions in family and marital dynamics, worse parent-child connections, diminished parenting effectiveness, and elevated parental stress, especially when ADHD coexists with behavioural disorders.[3]

Lower urinary tract symptoms (LUTS) include several manifestations, including voiding, storage, post-micturition, and discomfort, arising from disorders impacting the bladder and

urethra. Incontinence is categorised as diurnal incontinence and nocturnal incontinence. Children may have nocturnal incontinence with or without diurnal LUTS, including mono- vs non-monosymptomatic nocturnal enuresis. Daytime incontinence consists of incontinence due to urges, stress-related incontinence, and mixed incontinence.[4]

ADHD and LUTS are prevalent diseases in children, exhibiting significant co-occurrence and interactions. The incidence of ADHD among children and adolescents with LUTS is approximately 42.3 %.[5] Several lines of treatment are believed to have benefit for therapies of bladder dysfunction among children with both ADHD and LUTS. These include :Pharmacotherapy to primarily treat behavioral disorders such as: stimulants, SSRIs, traditional urotherapy (fundamental bladder advice), and medication are mainly used to address bladder dysfunction: anticholinergic agents.[6] Children might need pharmacological intervention to treat the behavioural problem, contingent upon the degree of their ADHD. It is unclear whether the ADHD and urinary incontinence share common central causes which affect both attention or lack of focus which led to the idea that effective therapy of ADHD may aid in managing the symptoms of bladder dysfunction.[7] A diverse array of pharmaceuticals, especially those utilised in behavioural regulation, is recognised to influence the urinary bladder and associated symptoms.[7] Children with ADHD often require a combination of drugs to regulate their behaviours, alongside non-pharmacological interventions.[8] The purpose of this work was to identify the different types of lower urinary tract dysfunction (LUTD) in children with ADHD and their responses to therapies.

Materials and methods

This prospective work had been conducted on children (6-18 years old), who fulfilled criteria for ADHD according to DSM-V with any type of LUTD and only naive patients who had no previous urological or psychiatric treatment. The study was done from June 2023 and February 2024 after approval of local ethical committee (36264MS72/2/23). Each relative of the patients provided a written well-informed consent.

Criteria for exclusion had been intelligence quotient (IQ) <70 %, individuals who have any medical condition that impacts cognitive function: hepatic, Renal, thyroid, connective tissue disorders, neurological disorders, diabetes mellitus, children with other urological abnormalities such as ureteropelvic junction obstruction and polyuria (due to diabetes insipidus, DM or other causes) or with urinary tract infection.

Each participant had been exposed to complete history taking, structured psychiatric interview for assessment of their psychiatric problems, laboratory investigations [urine analysis] and radiological investigations [Abdominopelvic ultrasound examination]. All patients were subjected to the following: The standard psychiatric treatment was initiated for every child according to psychiatrist point of view which was in form of: *Atomoxetine oral at a dosage of 0.5 mg/kg/day was used as initiation dose and gradually increased up to 1.8mg/kg as a maximum dose according to the response of each patient. *Methylphenidate (concerta©) oral at a dose 18 to 36 mg/day. Urological treatment in the form of urotherapy with initiation of psychiatric treatment. This form of treatment encompassed the following

five elements: information and clarification; elucidation on standard LUT function and the manner in which the youngster diverges from the norm, instructions about how to improve LUT dysfunction. In addition, patients with NE were advised to avoid drinking for 2 hours before bedtime, lifestyle recommendations include maintaining enough fluid intake and a balanced diet, establishing regular bladder and bowel emptying routines, documenting symptoms and voiding patterns employing bladder diaries or frequency-volume charts, and receiving support and motivation through consistent follow-up with a carer. Patients with monosymptomatic enuresis were treated initially using a combination therapy of 0.2 mg for desmopressin and 25 mg for imipramine which were taken one hour before bedtime. and patients with non-monosymptomatic enuresis were treated using combination therapy of oral desmopressin and solfenacin©. The initial daily doses were 0.2 mg for desmopressin 1 hour before bedtime and 5 mg for sofenacin suspension after breakfast.

Follow up: The patients were re-evaluated at 1,3,6 months to assess the improvement of the previously reported LUT symptoms. This evaluation was performed according to the following protocol: assessment of improvement of daytime symptoms like frequency, urgency and urge incontinence, Assessment of NE as following: [full response: 0-1 wet night during treatment, intermediate response: more than 50 % reduction of wet nights and no response: little or no effect]. the dose of desmopressin was increased to 0.3, 0.4 mg according to response of each patient. and the psychiatric symptoms were also monitored at the same time. Finally, both psychiatric and urological treatment were maintained for 6 months. Withdrawal of urological drugs. At 6 months, the urological drugs were gradually withdrawn, and LUT symptoms were re-evaluated at 2 weeks after cessation of these drugs. On the other hand, the psychiatric treatment was continued as prescribed before.

Statistical analysis

Data were input into the computer and analysed with IBM SPSS software version 20.0. (IBM Corporation, Armonk, New York) Qualitative data were represented utilising numerical values and percentages. The Shapiro-Wilk test has been employed to assess the normality of the distribution. Quantitative data has been defined by range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the findings obtained was judged at the 5 % level.

The Chi-square test has been utilised for categorical data to contrast various groups. Fisher's exact test: correction for chi-square when > 20 % of the cells have expected count < 5. Student t-test: for normally distributed quantitative parameters, to contrast between two studied groups

Results

This tudy enrolled 60 participants with a mean age 8.9±1.8 years. The demographic data, types of ADHD, types of LUTS and associated bowel symptoms are shown in (Table 1).

Table 1. Demographic data, types of ADHD and LUTS and associated bowel symptoms

		N= 60
Age (years) **<10 years** **≥ 10 years**		8.90±1.81 36 (60.0 %) 24 (40.0 %)
Sex	Male	42 (70.0 %)
	Female	18 (30.0 %)
Types of ADHD	Inattention	10 (16.7 %)
	Combined	38 (63.3 %)
	Hyperactivity	12 (20.0 %)
LUTS		
Enuresis	Monosymptomatic NE	42 (70.0 %)
	Non monosymptomatic (NE+diurnal symptoms)	18 (30.0 %)
Bowel symptoms		
Enuresis	Monosymptomatic NE	18 (30.0 %)
	Non monosymptomatic	4 (6.7 %)
Type of ADHD	Inattention	16 (26.6 %)
	Combined	6 (10.0 %)
	Hyperactivity	0 (00.0 %)

Data are presented as mean± SD or frequency (%). LUTS: Lower urinary tract symptoms, ADHD: attention deficit hyperactivity disorder, NE: Nocturnal Enuresis.

Forty two (70 %) cases were monosymptomatic NE. Full response was obtained in 28 (66.7 %) cases, 8(19.0 %) showed intermediate response and 6 (14.3 %) cases only did not show a response after 3 months of treatment. While 18 (30 %) cases were non-monosymptomatic, 14 (77.8 %) of them had a full response, 4 (22.2 %) cases had no response to treatment after 3 months. The response of enuresis treatment had no significant different between type of ADHD (Table 2).

Table 2. Response of enuresis treatment according to type of ADHD

		Response			FET	P
		No	Intermediate	Full		
Types of ADHD	**Inattention(n=10)**	2 (20.0 %)	0 (0.0 %)	8 (80.0 %)	5.279	0.217
	Combined(n=38)	4 (10.5 %)	6 (15.8 %)	28 (73.7 %)		
	Hyperactivity(n=12)	4 (33.3 %)	2 (16.7 %)	6(50.0 %)		

Data are presented as frequency (%). FET: Fisher's exact test, ADHD: attention deficit hyperactivity disorder.

No significant different existed between recurrence rate of NE and type of ADHD and NE (Table 3).

Table 3. Comparison of recurrence rate of NE according to the type of ADHD and NE

		Recurrence(n=42)		χ^2	P
Types of ADHD	**Inattention**	0 (0.0 %)		FET= 1.594	0.549
	Combined	6 (14.3 %)			
	Hyperactivity	2 (4.8 %)			
Type of enuresis	**Monosymptomatic NE**	34 (65.4 %)	8 (100.0 %)	3.956	^{FE}P=0.091
	Non monosymptomatic NE	18 (34.6 %)	0 (0.0 %)		

Data are presented as frequency (%). c^2: Chi-square test, FET: Fisher's exact test, NE: Enuresis.

Discussion

ADHD is a prevalent neurodevelopmental illness in children and adolescents, impacting around 5–10 % of school-aged individuals. Genetic deficit and particular brain malfunction may contribute to the development of ADHD. ADHD is concomitantly linked to several other disorders.[9] Numerous research have examined enuresis rates between children with ADHD and those without,[10,11] revealing that enuresis rates are elevated in children with ADHD.[12]

Studies reported that NE was common in male sex in children with ADHD. This agreed with our study in which male sex accounted for 70.0 % of patients. In a study which screened children with NE in ADHD, showed that combined and inattention type of ADHD are more frequent,[13] and another study found that only inattention type was more frequent in ADHD children with enuresis. [14] In our study , we reported that combined type was the commonest in ADHD with LUTS. In this article, among 60 children with ADHD, 42 (70.0 %) patients had mono-symptomatic NE, and 18 (30.0 %) patients had non-mono-symptomatic NE. Regarding the daytime symptoms, 18 (30.0 %) patients (non-mono-symptomatic NE) had frequency, urgency and urge incontinence. This agreed with. Mahjani B *et al.*[15] reported that urine storage symptoms (urine urgency, urinary frequency, dysuria) and voiding difficulties were the most often reported LUTS that co-occur with mental illnesses. Prior research indicated a significant prevalence of NE in children diagnosed with ADHD.[9,16,17] Moreover, the present study recorded 22 (73.2 %) patients with associated bowel symptoms (constipation), which was in agreement with McKeown *et al.*[18] that hypothesized increasing risk for functional constipation and faecal incontinence with ADHD. Long-acting formulations of MPH are the most often used FDA-approved medications for the management of ADHD. Despite the absence of established anti-enuretic effects of stimulants and their lack of indication for enuretic children without ADHD, there are case reports indicating remission of nocturnal enuresis with stimulant therapy.[19,20] Atomoxetine, a selective noradrenaline reuptake inhibitor, is useful in treating ADHD and might additionally positively influence control of the bladder in children with NE.[21] Urotherapy was used

in the current study in combination with other urological drugs to control the urinary symptoms. Von Gontard *et al.*[22] proposed that children with ADHD and bladder dysfunction ought to receive urotherapy to facilitate cooperation and adherence to further treatments for bladder dysfunction. Nonetheless, it has been noted that non-monosymptomatic NE has a suboptimal response to conventional urotherapy.[23] Regarding the response to treatment in the current study, 42 patients with mono-symptomatic NE were treated using combination therapy of oral desmopressin and imipramine drugs. They showed 66.7 % full response, 19 % intermediate response and 14.3 % no response. Shain S *et al.*[24] showed that the combined use of desmopressin and imipramine was more efficacious in alleviating monosymptomatic nocturnal enuresis, exhibiting a complete response rate superior to that of desmopressin and oxybutynin. Fujinaga S *et al.*[25] demonstrated that desmopressin monotherapy is no longer efficacious in managing bladder storage dysfunction and is linked to elevated recurrence rates upon discontinuation of the medication. Imipramine is a tricyclic antidepressant utilised for the management of ADHD. NE is proposed to be treated by three primary modes of action: alterations in arousal and sleep processes, sedative effects, and peripheral and central anticholinergic and spasmolytic properties. It may possibly function by enhancing the posterior pituitary production of ADH. Initial success rates are claimed to be as high as 50 %.[26] Imipramine has been shown to be successful in treating NE and may serve as a therapy choice for children with treatment-resistant NE who also have ADHD.[27,28] Administering a modest dosage (25 mg) of imipramine mitigates its possible negative effects, such as cardiotoxicity.[29] In the current study, 18 patients who had non-monosymptomatic NE in the present study, were treated using combination therapy with desmopressin and anti-cholinergic drug (solfinacine). They showed 14 (77.8 %) patients with full response and 4 (22.2 %) patients with no response. Anticholinergics are efficacious in managing bladder storage dysfunction in children, particularly daytime urinary incontinence. Nevertheless, anticholinergics are ineffective as monotherapy for the treatment of MNE.[30] In the study that was done by Cai T *et al.*[30] 30showed that desmopressin combined with anticholinergic agents is more effective in treating NE than desmopressin monotherapy. Ghanavati PM *et al.*[31] that was done on 62 child with non-monosymptomatic NE without ADHD symptoms, showed complete remission in 19 of 20 patients (95 %) in the group treated with desmopressin and solifenacin in comparison with monotherapy group. Regarding recurrence rate, in patients treated with desmopressin and Solifination showed no recurrence after cessation of treatment after 6 months in the present study .This was in agreement with Ghanavati PM *et al* .[31] showed no recurrence after 3 months of follow up. In the current study 8 of 42 participants with NE who had been managed with desmopressin and imipramine showed recurrence after gradual cessation of treatment. This was in agreement with Seyfhashemi M.[32] reported higher recurrence rate of both desmopressin and imipramine as a monotherapy. Gökçe Mİ *et al.*[33] showed that gradual withdrawal cessation of treatment was correlated with lower relapse rates contrasted to abrupt cessation and placebo.

The limitations of the study included that sample size had been relatively small. It was single center nonrandomized work and short term

follow up. Also, we didn't compare our results to the results of non-ADHD patients, and we did not have control group with placebo drugs. Thus, large-scale randomized comparative studies with longer follow up are encouraged to be designed so that our results can be verified with an increased statistical power.

Conclusions

Monosymptomatic NE is the commonest LUTS in ADHD children. Standard urotherapy and urological pharmaco-urotherapy beside psychiatric treatment have good response for treatment of LUTS in ADHD patients. A combination therapy of desmopressin and imipramine is an efficient treatment of monosymptomatic NE in ADHD children, while anticholinergic drugs plus desmopressin are effective in non-monosymptomtic NE. Gradual cessation of the urological pharmacotherapy should be done in continuation with standard psychiatric treatment is advised to decrease the recurrence rate.

CRediT Taxonomy

ME, SN: organized and designed the study.
MAH, OA, MA: drafted the manuscript and performed the statistical analysis.
ME: was responsible for the clinical assessment of the subjects and, together with SN, contributed to the interpretation of the results.
SN, MAH, OA, MA, ME: writing of the manuscript.
SN, MAH, OA, MA, ME: read and agreed the final version of the manuscript.

Competing interests

We have no competing interests.

Funding

We are self-funded

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