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Effects of methylphenidate on the lower urinary tract in patients with attention deficit hyperactivity disorder and without voiding dysfunction

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Summary

Background
Attention deficit hyperactivity disorder (ADHD) is characterised by a range of symptoms, such as excessive mobility, difficulty in maintaining attention and inadequate impulse control. Methylphenidate (MPH) is widely prescribed as a treatment for ADHD. In the literature, studies investigating the effects of MPH on the lower urinary tract (LUT) are limited.

Objective
The aim of the study was to evaluate MPH-induced LUT symptoms (LUTSs) in patients with ADHD without a diagnosis of voiding dysfunction (VD).

Study design
After ethical committee approval, volunteers aged 7–17 y were divided into two groups, with group 1 composed of individuals diagnosed with ADHD but not VD and group 2 (control) composed of healthy individuals. Lower urinary tract symptoms and quality of life, in addition to uroflowmetry test results and postvoiding residual volume (PVRV), were evaluated in both groups at baseline and again 4 wk later. The individuals in group 1 were treated with MPH after baseline screening. The dysfunctional voiding scoring system questionnaire was used for scoring LUTSs. Postvoiding residual volume was measured by ultrasound. Bladder capacity (BC) was calculated as the sum of voided volume (VV) and PVRV. The means of the maximum flow rate (Q max), mean flow rate (Q mean), VV, PVRV and BC were recorded.

Results
After exclusions, there were 43 participants in group 1 and 39 participants in group 2. There was no significant difference between the mean age of groups ($p = 0.727$). Compared with the baseline, VV and BC increased significantly in group 1 ($p = 0.001$ and $p = 0.002$, respectively) at the 4-wk follow-up. There was no significant difference in these parameters in group 2.

Discussion
This study demonstrated that VV and BC increased after MPH treatment in patients with ADHD without a diagnosis of VD. The mechanism underlying this effect is unclear, but it may be associated with dopaminergic and noradrenergic effects.

Conclusion
The findings of the present study can inform further studies on the mechanism underlying the effect of MPH on the LUT. In a future study, the authors suggest evaluating the effects of MPH in a urodynamic study in patients with ADHD diagnosed with VD.

Summary Table The significant results of the study group (group 1).

Evaluated parameters	Initial (mean ± SD); (n = 43)	4th week (mean ± SD); (n = 43)	p value
VV (ml)	216.86 ± 36.63	232.09 ± 37.48	**0.001***
BC (ml)	222.79 ± 38.85	237.09 ± 39.45	**0.002***

VV = voided volume; BC = bladder capacity; SD = standard deviation. * Bolded results are statistically significant p values.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is characterised by a range of symptoms, such as excessive mobility, difficulty in maintaining attention and inadequate impulse control [1]. Its prevalence is reported to be 3–5% in childhood, and it is 3–10 times more common in boys than in girls [2,3]. The prevalence of ADHD in the US among children aged 4–7 y was reported to be 11% [4]. Methylphenidate (MPH) is widely prescribed as a treatment for ADHD [3]. Previous research showed that MPH was effective in the treatment of giggle incontinence (GI) [5,6]. The mechanism underlying this effect is not clear. In the literature, studies investigating the effects of MPH on the lower urinary tract (LUT) are limited.

In recent years, the dysfunctional voiding scoring system (DVSS) questionnaire was developed for use in the paediatric population. The questionnaire is similar to the International Prostate Symptom Score questionnaire for adults [7,8]. The DVSS questionnaire focusses on LUT symptoms (LUTSs), as well as quality of life (QoL), and provides a facile method for the diagnosis of voiding dysfunction (VD).

Uroflowmetry can help evaluate the LUT. It is a simple, fast, cost-effective and non-invasive test that is frequently used to assess urine flow parameters in urology practice [9]. Uroflowmetry can provide information about the maximum (Q_{max}) and mean (Q_{mean}) urinary flow rate, voided volume (VV) and the duration of voiding. After urination, the postvoiding residual volume (PVRV) can be measured using an ultrasound device. Uroflowmetry is not sufficient to determine the source of the pathology. The latter requires a urodynamic study (UDS). However, uroflowmetry is much shorter, simpler, cost-effective and non-invasive than a UDS, which has led to the frequent use of this test.

According to previous experimental studies, MPH increased bladder capacity (BC), VV and the micturition interval in rats [10,11]. There are only a few studies on the effects of MPH on LUTSs in humans. The aim of the present study was to evaluate the effects of MPH on the LUT in patients with ADHD without a diagnosis of VD based on their DVSSs, QoL and uroflowmetry parameters. The hypothesis was that MPH would have an effect on the LUT.

Methods

This prospective study was approved by the Ethics Committee of Erzurum Ataturk University Medical Faculty. The study was conducted in the Agri State Hospital Department of Urology and Child and Adolescent Psychiatry between April and September 2018. The nature of the study was explained to the volunteers and their parents. Informed consent was obtained from the parents of the volunteers who agreed to participate in the study.

Volunteers aged 7–17 y were divided into two groups. The study group (group 1) consisted of patients without a diagnosis of VD who were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and treated with MPH (0.5 mg/kg) after baseline screening. The appropriate dose adjustment of MPH for patients with ADHD was made by psychiatrists according to the patients' weights and other conditions. The control group (group 2) consisted of healthy volunteers with no known major health problems or a diagnosis of VD and no neurological or psychiatric disorders.

In both groups, LUTSs, QoL, uroflowmetry test results and PVRVs were evaluated. The DVSS questionnaire was used for scoring LUTSs [7] (Fig. 1). In each participant, urinalysis (UA) (included urine microscopy) was performed to detect any urinary abnormalities. Uroflowmetry was performed using a classic uroflowmetry device (Flowstar®; Medical Measurement Systems, Enschede, the Netherlands). Uroflowmetry was conducted when the volunteers felt the urge to void. Postvoiding residual volume was measured using an ultrasound device (Mindray DC-3; Diagnostic Ultrasound Systems, Shenzhen, China). Bladder capacity was evaluated as the sum of VV and PVRV. The means of the Q_{max}, Q_{mean}, VV, PVRV and BC were recorded.

Those with VD (DVSS $>$ 8), systemic diseases, neurological or psychiatric disorders, a history of ADHD drug use, medication use for reasons other than ADHD and abnormal UA findings (leucocyturia, erythrocyturia, haemoglobinuria and so on) were excluded. Volunteers who were unable to perform uroflowmetry, unable to attend the hospital for follow-up or who were non-compliant were also excluded. After 4 wk, with the exception of UA, the same tests administered at baseline were repeated in the two groups.

Statistical analysis

The Statistical Package for Social Sciences (version 22.0) was used to perform the statistical analysis. A paired sample *t*-test was used to compare differences in the measured parameters at baseline compared with those at the 4-wk follow-up, and an independent *t*-test was used to compare between-group differences in the ages of the groups. A value of $p < 0.05$ was considered statistically significant.

Results

At study commencement, there were 89 participants in group 1 and 79 participants in group 2. After baseline evaluation and initial exclusions, there were 64 participants in group 1 and 61 participants in group 2 (Fig. 2). The demographics of the study sample after all exclusions were as follows: 34 boys (70.9%) and 9 girls (29.1%) in group 1 ($n = 43$), with a mean age (year ± standard deviation [SD]) of 11.84 ± 2.83 y and 28 boys (71.8%), and 11 girls (28.2%) in group 2 ($n = 39$), with a mean age (year ± SD) of 11.25 ± 2.56 y. There was no significant between-group difference in terms of age ($p = 0.727$). Comparison of the baseline and 4-wk results showed that VV and BC increased significantly in group 1 ($p = 0.001$ and $p = 0.002$, respectively) (Table 1). There was no significant difference in any of the measured parameters in group 2 at the 4-wk follow-up (Table 2).

Does your child have urinary incontinence (peeing not on the toilet) during the day?	No	Sometimes	1-2 times/day	3 or more times/day
	0	1	3	5
If yes to Question 2	A few drops	Only underwear wet		Outer clothing layers wet
	1	3		5
Does your child have urinary incontinence (peeing not on the toilet) during the night?	No	1-2 nihgts/week	3-5 nights/week	6-7 nights/week
	0	1	3	5
If yes to Question 4	Underwear or pajamas wet		Bed wet	
	1		4	
My child goes to toilet to pee..	Less than 7 times/day		7 or more times/day	
	0		1	
My child has to strain to pee	No		Yes	
	0		3	
My child experiences pain when s/he pees	No		Yes	
	0		1	
My child pees intermittently when on the toilet	No		Yes	
	0		2	
My child has to go to revisit to toilet to pee soon after s/he pees	No		Yes	
	0		2	
My child has to run to the toilet when s/he feels the need to pee	No		Yes	
	0		1	
My child can hold his/her pee by crossing his/her legs, squatting, or doing the "pee dance".	No		Yes	
	0		2	
My child wets his/her clothes before reaching the toilet	No		Yes	
	0		2	
My child does not pass stool every day	No		Yes	
	0		2	
Quality of life				
If your children experiences any of the symptoms/issues mentioned above, does this affect his/her family life or social life?	Not at all	Not so much	Affects	Seriously affects
	0	1	3	5

Fig. 1 The dysfunctional voiding scoring system questionnaire for children [7].

Discussion

The mechanism of ADHD may be related to noradrenergic and dopaminergic pathways in the central nervous system (CNS), with ADHD thought to cause a decrease in adrenergic activity in the CNS [12,13] and thus affect the LUT [14]. As reported previously, a decrease in the β-adrenergic effect leads to detrusor contraction, whereas an increase leads to detrusor relaxation [15]. An increase in the frequency of LUTSs was previously reported in patients with ADHD [16]. Research also demonstrated that MPH, which belongs to a class of psychostimulant drugs, acted by dopaminergic and noradrenergic reuptake blockade in the CNS [17,18]. The effect of MPH on ADHD is hypothesised to work in a similar way. Previous studies reported the effectiveness of MPH as a treatment for GI and enuresis nocturna (EN) [5,6,19,20], thereby clearly pointing to its potential effects on the LUT.

In experimental animal studies, researchers investigated the effects of MPH on the LUT. Choi et al. [10] administered MPH (1.25 mg/kg) intragastrically to healthy mice and compared urodynamic parameters before and after MPH administration. They reported that the MPH treatment had no impact on PVRV but that it significantly increased VV and BC. They reported no change in PVRV but significant increases in VV and BC. To validate their findings, the authors suggested that a similar study be performed in children with ADHD receiving MPH treatment. Kim et al. [11] conducted a similar study investigating the effects of MPH on urodynamic parameters in spontaneous hypertensive mice. In their study, intragastric MPH (6 mg/kg) did not affect PVRV but led to a significant increase in VV and BC. They

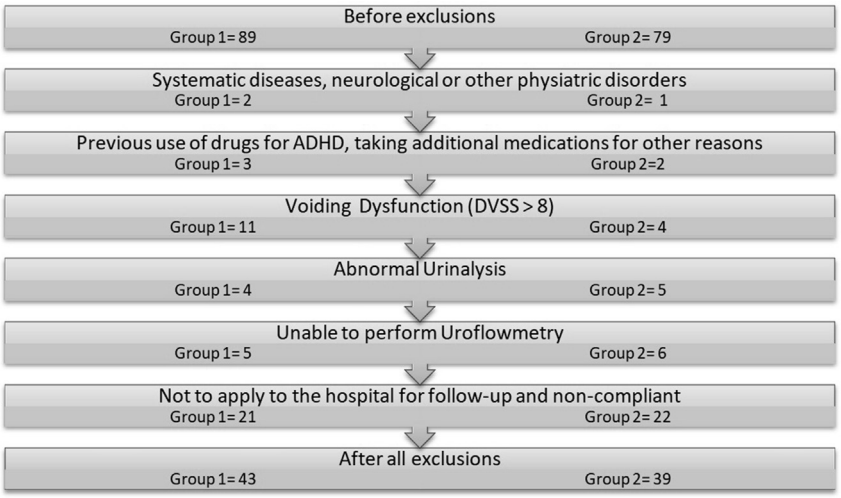

Fig. 2 Demonstration of excluded volunteers and reasons by a flowchart diagram. ADHD = attention deficit hyperactivity disorder; DVSS = dysfunctional voiding scoring system.

concluded that the peripheral nervous system, as well as the CNS, in patients with ADHD treated with MPH may play an important role in the LUT. The findings of these two studies on the effect of MPH on PVRV, VV and BC support those of the present study. Both studies also reported that the micturition interval, which is known to be strongly correlated with BC, increased significantly after MPH administration.

However, some studies reported that MPH had no effect on BC. Chang et al. [5] reported 1-y UDS changes in nine girls who had a diagnosis of GI and received treatment with 5 mg of MPH. They found MPH treatment had no impact on Q_{max} values or BC. The MPH treatment significantly increased both maximum urethral closure pressure and maximum urethral pressure. They suggested that this effect was related to dopaminergic effect and MPH could be used to treat GI.

A number of studies have investigated the impact of psychotropic drug administration on the LUT. In an acetic acid—induced bladder irritation model in female cats, Thor

Table 1 The results of study (ADHD) group (group 1).

Evaluated parameters	Initial (mean ± SD); (n = 43)	4th week (mean ± SD); (n = 43)	p value
Q_{max} (ml/sec)	21.73 ± 5.42	21.27 ± 5.61	0.416
Q_{mean} (ml/sec)	11.79 ± 3.15	11.85 ± 3.03	0.390
VV (ml)	216.86 ± 36.63	232.09 ± 37.48	**0.001***
PVRV (ml)	5.93 ± 12.59	5.00 ± 12.63	0.253
BC (ml)	222.79 ± 38.85	237.09 ± 39.45	**0.002***
DVSS	3.23 ± 2.66	3.09 ± 2.73	0.204
QoL	0.48 ± 0.66	0.37 ± 0.61	0.168

ADHD = attention deficit hyperactivity disorder; Q_{max} = maximum flow rate; Q_{mean} = mean flow rate; VV = voided volume; BC = bladder capacity; PVRV = postvoiding residual volume; DVSS = dysfunctional voiding scoring system; QoL = quality of life, SD = standard deviation.. * Bolded results are statistically significant p values.

Table 2 The results of the control group (group 2).

Evaluated parameters	Initial (mean ± SD); (n = 39)	4th week (mean ± SD); (n = 39)	p value
Q_{max} (ml/sec)	21.41 ± 6.00	21.62 ± 5.07	0.394
Q_{mean} (ml/sec)	11.59 ± 2.95	11.74 ± 2.76	0.087
VV (ml)	239.48 ± 37.95	236.61 ± 25.85	0.383
PVRV (ml)	8.07 ± 13.93	6.15 ± 12.95	0.075
BC (ml)	247.56 ± 41.51	242.76 ± 38.77	0.215
DVSS	2.64 ± 2.38	2.69 ± 2.30	0.534
QoL	0.35 ± 0.58	0.25 ± 0.44	0.103

Q_{max} = maximum flow rate; Q_{mean} = mean flow rate; VV = voided volume; BC = bladder capacity; PVRV = postvoiding residual volume; DVSS = dysfunctional voiding scoring system; QoL = quality of life; SD = standard deviation.

and Katofiasc [21] reported that duloxetine, a serotonin and noradrenaline reuptake inhibitor, increased BC. In a study that used the same bladder model, Katofiasc et al. [22] reported that duloxetine combined with another serotonin and noradrenaline reuptake inhibitor, venlafaxine, significantly increased BC in female cats. In a patient who has diagnosis of ADHD and EN, Bahali et al. [20] reported that EN, as well as ADHD symptoms, responded to MPH treatment. In the same case, when MPH was replaced with atomoxetine, a selective noradrenaline reuptake inhibitor, EN responded to the atomoxetine treatment. The authors suggested that the positive effects of MPH and atomoxetine on EN may be due to these drugs reducing bladder contractility and enhancing detrusor BC by increasing noradrenergic effects. However, Katofiasc et al. [22] reported that the selective noradrenaline reuptake inhibitor thionisoxetine had no effect on BC and that the selective serotonin reuptake inhibitor S-norfluoxetine significantly increased BC. In the same study, a combination of thionisoxetine and S-norfluoxetine had no effect on BC [22].

According to most studies in the literature and this study, MPH appears to increase BC. It may be explained by a β-adrenergic effect of MPH on the detrusor muscle, leading to relaxation of the detrusor muscle and increased BC. However, as noted previously, some studies do not support this idea. The mechanism underlying the effect of MPH on the LUT remains unclear. To enhance understanding of this mechanism, the effects of MPH in patients with ADHD and VD (DVSS $>$ 8) and in patients with LUTSs (e.g. incontinence, an overactive bladder and EN) without a diagnosis of ADHD could be studied. Urodynamic studies of such patients would provide more reliable results than uroflowmetry. In addition, studies on the expression of receptors or the alteration of neurotransmitters in the LUT after MPH administration would help shed light on the mechanism underlying the effect of MPH on the LUT.

There were some limitations in this study. First, LUTSs were assessed by uroflowmetry rather than the UDS, which is the optimum protocol for evaluating LUTSs. It would be better to compare the results with the UDS rather than with uroflowmetry. Second, none of the participants in the present study had a diagnosis of VD. The inclusion of patients with ADHD with a diagnosis of VD would provide valuable results to see the effects of MPH on LUTSs. Third, the authors did not compare the outcomes of different doses of MPH, and different doses might have altered the outcomes. Finally, the duration of the MPH treatment was short (4 wk). The long-term effects of MPH administration on the LUT may differ from the short-term effects observed herein.

Conclusion

To the authors' knowledge, this is the first study to investigate the effects of MPH on the LUT in children with ADHD without a diagnosis of VD. The authors found that MPH increased VV and BC in these patients. The findings of this study may aid future studies aimed at understanding the mechanism underlying the effects of MPH on the LUT. Although there were statistically significant increases in VV and BC in these patients, these may not result in clinically significant improvements in LUTSs in patients with ADHD diagnosed with VD. To enhance the reliability of the study findings, the authors suggest evaluating the effects of MPH on LUTSs in patients with ADHD diagnosed with VD in a UDS.

Author statements

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Ethical approval

The study protocol was approved by the Erzurum Ataturk University Ethical Committee (approval number: B.30.2.ATA.0.01.00).

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Competing interests

The authors declare that there is no conflict of interest.

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