Received: 21 May 2023 | Accepted: 16 August 2023

DOI: 10.1002/nau.25269

CLINICAL ARTICLE

Neurourology Urodynamics | SUFU | WILEY

The association of urinary BDNF, ATP, and MMP-2 with bladder compliance in children with myelodysplasia

Cagri Akin Sekerci MD[1] | Mehmet Umut Kutukoglu MD[2] | Banu Isbilen Basok MD[3] | Mesut Fidan MD[3] | Sebahat Cam MD[4] | Selcuk Yucel MD[1] | Tufan Tarcan MD, PhD[1,5]

[1]Department of Urology, Division of Pediatric Urology, School of Medicine, Marmara University, Istanbul, Turkey

[2]Department of Urology, School of Medicine, Marmara University, Istanbul, Turkey

[3]Department of Biochemistry, Tepecik Training and Research Hospital, University of Health Sciences, Izmir, Turkey

[4]Department of Pediatric Gastroenterology, School of Medicine, Medeniyet University, Istanbul, Turkey

[5]Department of Urology, School of Medicine, Koç University, Istanbul, Turkey

Correspondence
Tufan Tarcan MD, PhD, Fevzi Çakmak Mah., Muhsin Yazicioglu Cad. No:10 Ust Kaynarca/Pendik/Istanbul, Turkey.
Email: bilgi@tufantarcan.com

Funding information
Marmara University, School of Medicine Foundation

Abstract

Aim: The purpose of our study was to evaluate the relationship of urinary brain-derived neurotrophic factor (BDNF), adenosine triphosphate (ATP), matrix metallopreteinase-2 (MMP-2) with urodynamic findings and upper urinary tract deterioration (UUTD) in children with myelodysplasia.

Materials and Methods: Children with myelodysplasia evaluated in outpatient clinic between 2022 and 2023 were included. All patients underwent urinary ultrasonography, voiding cystourethrography, urodynamics, and DMSA scintigraphy. Urine samples were collected before urodynamics. Control urine was collected from 10 healthy children. Urinary biomarker values of patients and controls were compared, and subgroup analysis was performed.

Results: The median age of 40 children (26 girls) included in the study was 108 (8–216) months, and the control group (six girls) was 120 (60–154) ($p = 0.981$). Urinary BDNF, MMP-2, and ATP were found to be significantly higher in children with myelodysplasia compared to the control ($p = 0.007$, $p = 0.027$, $p = 0.014$, respectively). The three biomarker values were similar in children with bladder compliance below or above 10 cmH2O/mL ($p = 0.750$, $p = 0.844$, $p = 0.575$). No difference was found in terms of UUTD in all three biomarkers ($p = 0.387$, $p = 0.892$, $p = 0.705$). A negative correlation was found between urinary ATP and compliance ($p < 0.05$).

Conclusion: In this study, all three biomarkers were found to be higher in children with myelodysplasia than in controls. There was a negative correlation between urinary ATP and compliance. Urinary biomarkers may contribute the follow-up of children with neurogenic lower urinary tract deterioration in future with their noninvasive features. However, the lack of standardization and the inability to reliably predict risky groups are important shortcomings of urinary biomarkers.

KEYWORDS
ATP, BDNF, children, MMP-2, myelodisplasia, urodynamics

1 | INTRODUCTION

Spina bifida is the most common cause of neurogenic lower urinary tract (LUT) dysfunction in children, and the most important goal in treatment and follow-up is the protection of upper urinary tract (UUT). Immediate postnatal primary repair and proactive approach, which includes early clean intermittent catheterization (CIC) and anticholinergic treatment are the factors that play an important role in the prevention of UUT.[1] Urodynamic studies are accepted the gold standard method in both treatment planning and monitoring of children with neurogenic LUT dysfunction by most of authors and provides quantitative parameters about bladder functions.[2] In recent years, several studies have been published on the supportive effects of various urinary biomarkers, which stand out with their easy measurable properties in diagnosis and follow-up. Although urinary biomarkers are promising in clinical evaluations besides urodynamics, their use in clinical practice is not recommended today due to lacks in their standardization, inconsistent results between studies, and negative results in subgroup analyses.[3] Among these urinary biomarkers, the most frequently studied is Nerve Growth Factor (NGF), and to the best of our knowledge, other evaluated biomarkers in children with neurogenic lower urinary tract deterioration (LUTD) dysfunction are brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF) Beta-1, and tissue inhibitor matrix metalloproteinase-2 (TIMP-2).[4,5] In our review, we found that urinary biomarkers were studied more in patients with nonneurogenic LUTD or in adults. In this study, we aimed to evaluate the relationship of three biomarkers (two previously unstudied in children) with urodynamic findings and UUT damage in children with myelodysplasia. One of them is matrix metallopreteinase-2 (MMP-2), which has been shown to be associated with poor bladder compliance in adults with spina bifida[6]; and the other is urinary adenosine triphosphate (ATP), which has been reported to be associated with detrusor overactivity in women with overactive bladder.[7] The last one is urinary BDNF, which was previously shown to be reduced by intravesical injection of botulinum toxin in children with myelodysplasia.[5]

2 | MATERIALS AND METHODS

Children with myelodysplasia evaluated in the pediatric urology outpatient clinic between 2022 and 2023 were included in the study. Ethical approval was obtained from the local ethics committee (Marmara University) before the study (No: 09.2021.250). Informed consent forms were obtained from all parents. All patients underwent urinary ultrasonography, voiding cystourethrography, urodynamic studies, and DMSA renal scintigraphy. Children with missing data were excluded from the study. Urodynamic studies and reporting were performed according to the recommendations of the International Children's Continence Society.[8] Locum Wireless Urodynamic System (Aymed) was used. Urodynamic studies were performed when the urine culture was sterile, with adequate bowel cleanout. Urodynamic studies were not performed in the presence of urinary tract infection (UTI), bacteriuria, leukocyturia, and hematuria. Urine samples were collected into sterile urine collection tubes before urodynamics in all patients. As a control group, midstream morning urine samples were collected from 10 healthy children. After each urine sample was centrifuged at 3000 g for 10 min the supernatant was aliquoted in 1.5-mL microcentrifuge tubes and stored at −80°C until further analysis. Constipation status was evaluated with the Bristol stool chart.

Urinary biomarker values of patients and controls were compared, and subgroup analysis was performed in the myelodysplasia group in terms of urodynamic findings and upper urinary tract deterioration (UUTD). The presence of renal scar, vesicoureteral reflux (VUR), or hydronephrosis (HN) was considered as UUTD. Expected bladder capacity (EBC) for age was calculated with the formula $(\text{age} \times 30) + 30$. Detrusor leak point pressure was defined as the detrusor pressure at the time of the urine leakage without the abdominal pressure increase and the involuntary detrusor contraction.[8] In this study, the cut-off value for bladder compliance was accepted as 10 cmH2O/mL, since the number of patients with compliance above 20 cmH2O/mL ($n = 5$) was insufficient for statistical analysis.

2.1 | Biochemical analyses

BDNF levels in supernatants were measured by using a commercial ELIZA kit (RayBiotech Inc.; Catalog No: ELH-BDNF; Lot No: 0622210106). The analytical sensitivity of the assay was 80 pg/mL. The intra- and interassay coefficients of variability (CV) of the test were under 10% and 12%, respectively. Urinary MMP-2 levels were analyzed with an ELIZA method (Elabscience Inc.; Catalog No: E-EL-H1445; Lot No: BK8XHASCT4). The analytical sensitivity of the assay was 0.47 ng/mL. Both CVs were under 10%. Urine ATP levels were measured using an ELIZA kit manufactured by MyBioSource Inc. (Catalog No: ELH-BDNFMBS2887427; Lot No: 1G015C). The intra- and interassay CVs of the test were under 5.9%

and 10.1%, respectively. The analytical sensitivity of ATP test was <0.35 ng per mL. Urinary creatinine (Cr) concentration was determined on each sample using kinetic Jaffe method in the AU5800 clinical chemistry system (Beckman Coulter Inc.). The urinary concentrations of BDNF, MMP-2, and ATP were normalized to the concentration of urinary Cr and results were expressed as nanograms (or picograms) per milligram of Cr.

2.2 | Statistical analyses

Data were analyzed using the IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Statistics for Windows). The normality of the distribution of the variables was evaluated using the Shapiro–Wilk test. As the distribution of continuous variables did not show a normal distribution, continuous data were presented with median, minimum, and maximum. Comparisons of independent and dependent groups were done with the Mann–Whitney U test and Wilcoxon signed ranks test, respectively. Correlation analysis was done with the Spearman correlation test. $p < 0.05$ was considered statistically significant. G Power program was used for power analysis. Power analysis was performed according to the study of Silva-Ramos et al. [7] for urinary ATP and according to the study of Ozdemir et al. for urinary BDNF.[9]

3 | RESULTS

The median age of 40 children (26 girls [65%], 14 boys [35%]) included in the study was 108 (8–216) months, and the control group (6 girls, 4 boys) was 120 (60–154) months ($p = 0.981$). The primary etiology of 35 children was myelomeningocele (87.5%), two dermal sinus (5%), two tethered cord (5%), and one sacrococcygeal immature teratoma (2.5%). A total of 38 (95%) patients were under CIC and anticholinergic therapy, and 33 (82.5%) patients were receiving antibiotic prophylaxis. Four (10%) of the patients had unilateral HN, eight (20%) had bilateral HN; five (12.5%) had unilateral VUR (two low grade, three high grade), four (10%) had bilateral VUR (four low grade–high grade); 12 (30%) had a renal scar on DMSA scintigraphy. Urinary BDNF, MMP-2, and ATP were found to be significantly higher in children with myelodysplasia compared to the control group ($p = 0.007$, $p = 0.027$, $p = 0.014$, respectively) (Table 1, Figure 1). The patients' maximum cystometric capacity (MCC) was 179 (31–554) mL, maximum detrusor pressure was 44.50 (3–187) cmH2O, and MCC/EBC was 52.83 (15–168) %. In the subgroup analysis, the three biomarker values were similar in children with bladder compliance below or above 10 cmH2O/mL ($p = 0.750$, $p = 0.844$, $p = 0.575$) (Table 2). In addition, no difference was found in terms of UUTD in three biomarkers ($p = 0.387$, $p = 0.892$, $p = 0.705$) (Table 2, Figure 1). Although there was no correlation between detrusor pressure, MCC/EBC, and urinary biomarkers, a negative correlation was found between ATP and bladder compliance in the correlation analysis ($p < 0.05$) (Table 2). Interestingly, a positive correlation was detected among the three biomarkers ($p < 0.01$) (Table 3, Figure 2). There was no significant difference in urinary biomarkers between children with and without constipation ($p = 0.552$).

TABLE 1 Comparison of urinary BDNF, ATP, and MMP-2 values between patients and controls.

	Patients ($n = 40$) median (min–max)	Control ($n = 10$) median (min–max)	p Value
Age (month)	108 (8–216)	120 (60–154)	0.981
BDNF (ng/mg Cr)	1.25 (0.04–37.95)	0.20 (0.03–3.29)	0.007
MMP-2 (ng/mg Cr)	4.78 (0.73–24.59)	2.68 (0.66–4.37)	0.027
ATP (ng/mg Cr)	17.70 (2.92–123.95)	10.75 (3.09–16.52)	0.014

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; MMP-2, matrix metallopreteinase-2.

A total of 40 patients and 10 healthy controls at $\alpha = 0.05$ error level provided 1.00 power for urinary ATP and 0.93 for urinary BDNF. Power analysis for urinary MMP-2 could not be performed because there was no study with a healthy control group.

4 | DISCUSSION

Biomarkers are measurable structures used to evaluate physiological or pathological processes or monitor response to treatment. It can be in the form of protein and carbohydrate, as well as in a genetic or metabolite product. Apart from urological conditions, biomarkers are studied intensively in many different disciplines such as neurology, endocrinology, oncology, psychiatry, and cardiology. The main purpose of concentrating on examining the efficacy of biomarkers and searching for new ones seems to be the need for easily measurable, simple, effective, and inexpensive tests in the diagnosis and follow-up of diseases. In urology, the evaluation of the relationship between bladder dynamics and biomarkers is one of the current and prominent areas.

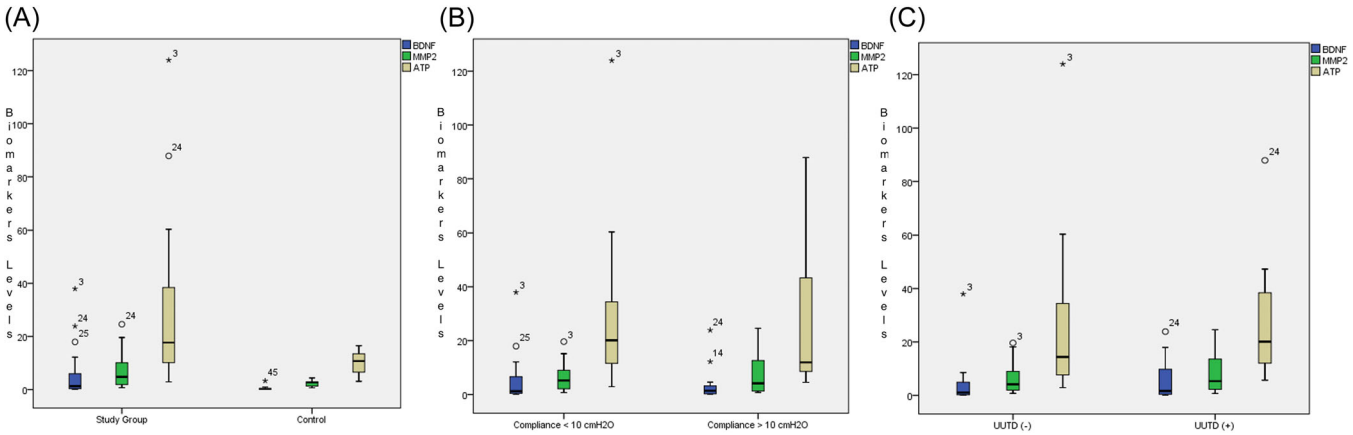

FIGURE 1 Boxplots of urinary brain-derived neurotrophic factor (BDNF), adenosine triphosphate (ATP), and matrix metallopreteinase-2 (MMP-2) levels (ng/mg Cr) according to study groups and controls (A); bladder compliance (B); upper urinary tract deterioration (UUTD) (C).

TABLE 2 The values of urinary biomarkers in terms of bladder compliance and UUTD.

	Compliance < 10 cmH2O/mL ($n = 29$) median (min–max)	**Compliance > 10 cmH2O/mL ($n = 11$) median (min–max)**	***p* Value**
BDNF (ng/mg Cr)	1.24 (0.04–37.95)	1.39 (0.08–23.88)	0.750
MMP-2 (ng/mg Cr)	5.22 (0.73–19.62)	4.15 (0.76–24.59)	0.844
ATP (ng/mg Cr)	20.12 (2.92–123.95)	11.93 (4.51–87.89)	0.575
	UUTD (+) ($n = 20$) median (min–max)	**UUTD (-) ($n = 20$) median (min–max)**	***p* Value**
BDNF (ng/mg Cr)	1.46 (0.08–23.88)	1.16 (0.04–37.95)	0.387
MMP-2 (ng/mg Cr)	5.28 (0.73–24.59)	4.13 (0.76–19.62)	0.892
ATP (ng/mg Cr)	19.41 (4.96–87.89)	15.54 (2.92–123.95)	0.705

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; MMP-2, matrix metallopreteinase-2; UUTD, upper urinary tract deterioration.

Although invasive urodynamic studies are the most important test for evaluating LUT functions, researchers have turned to the development of ancillary tests because of their sophistication. Studies investigating the relationship between urinary biomarkers and LUT dysfunction are more common in adults but are limited in children, particularly in neurologic LUT dysfunction. To our knowledge, urinary biomarkers have been evaluated in only five studies in children with neurological LUT dysfunction. In these studies, it was reported that urinary NGF, TGF Beta-1, TIMP-2 were correlated with urodynamic parameters such as detrusor leak point pressure, and the levels of urinary NGF, TGF Beta-1, and BDNF decreased after intravesical botulinum injection. In the present study, urinary ATP, MMP-2, and BDNF were studied for the first time in children with myelodysplasia and age-matched healthy children.

It is thought that ATP, which has been shown to be secreted from bladder urothelium cells,[10] provides a link between bladder tension and sensory nerves.[11] It is known that urinary ATP is released with stimuli such as bladder tension,[10] capsaicin, and acid.[12] There is numerous evidence that ATP is closely related to bladder functions. In experimental studies, it has been shown that urinary ATP is increased in spinal cord trauma,[13] interstitial cystitis,[14] and inflammation[15] models. In the study of Cheng et al., a negative correlation was reported between voided volume, the first desire to void, and ATP in voided urodynamic fluid in patients with urodynamically proven detrusor overactivity.[16] However, in the same study, no relationship was found between detrusor pressures and ATP during filling and voiding. In addition, in the control group, it was reported that there was a reverse correlation between ATP and MCC. ATP levels were similar in patients and controls. The authors interpreted these findings as ATP may play a role in the etiology of urgency in patients. They also emphasized that it may have a normal physiological role by

TABLE 3 Correlations for bladder compliance, maximum detrusor pressure, MCC/EBC, ATP, BDNF, and MMP-2 in patients.

	Compliance (cmH2O/mL)	pDetmax (cmH2O)	EBC/MCC (%)	ATP (ng/mg Cr)	BDNF (ng/mg Cr)	MMP-2 (ng/mg Cr)
Compliance (cmH2O/mL)	1.00	−0-584**	−0.601**	−0.331*	−0.208	−0.237
pDetmax (cmH2O)	−0-584**	1.00	−0.133	0.106	−0.189	−0.045
EBC/MCC (%)	−0.601**	−0.133	1.00	−0.139	−0.289	−0.159
ATP (ng/mg Cr)	−0.331*	0.106	−0.139	1.00	0.635**	0.892**
BDNF (ng/mg Cr)	−0.208	−0.189	−0.289	0.635**	1.00	0.626**
MMP-2 (ng/mg Cr)	−0.237	−0.045	−0.159	0.892**	0.626**	1.00

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; MCC/EBC: maximum cystometric capacity/expected bladder capacity; MMP-2, matrix metallopreteinase-2; pDetmax: maximum detrusor pressure during filling.

*Spearman correlation test, $p < 0.05$

**$p < 0.01$.

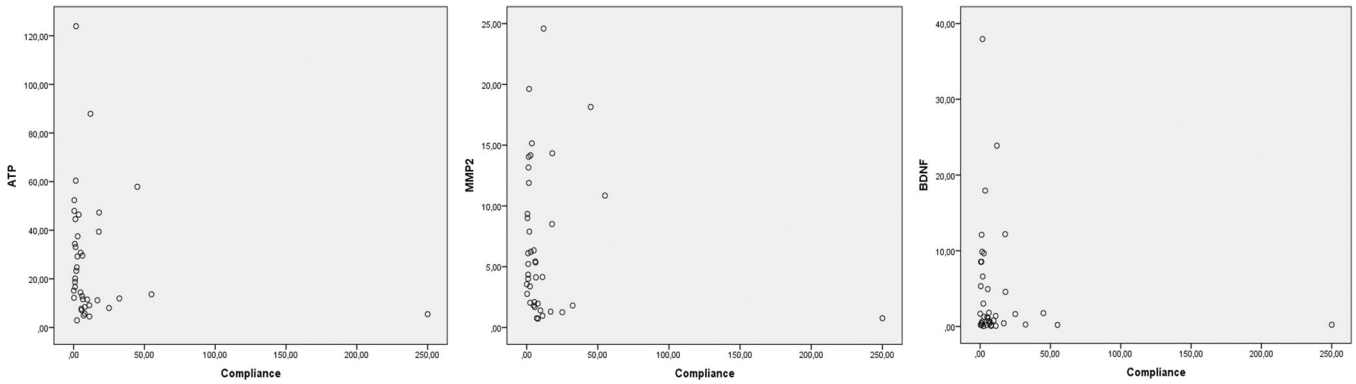

FIGURE 2 Boxplot charts between urinary adenosine triphosphate (ATP), matrix metallopreteinase-2 (MMP-2), brain-derived neurotrophic factor (BDNF), and bladder compliance.

regulating the feeling of bladder filling. The same research team found a negative correlation between ATP in voiding urodynamic fluid and urine pH in another study they conducted in women with overactive bladder.[17] In another study, urinary ATP was reported to be a highly sensitive dynamic biomarker for detrusor overactivity in women with overactive bladder (the area under the curve = 0.7407; 95% confidence interval = 0.62–0.86; $p = 0.001$).[7] In this study, urinary ATP was found to be significantly higher in children with myelodysplasia compared to the healthy control group. Moreover, it shows an inverse correlation with bladder compliance, which is one of the most important urodynamic parameters in neurogenic bladder dysfunction. Similar to the literature, no significant relationship was found between detrusor pressures and ATP. Since there were children from different age groups in our study, we used and analyzed the bladder capacity as MCC/EBC. We did not find a significant relationship between MCC/EBC and ATP, unlike the study of Cheng et al.[16] However, the patient population (children and adult) and pathological mechanisms (neurogenic and nonneurogenic) of the two studies are different. Unfortunately, there is no comparable study in the literature that was performed in a similar patient group.

The MMP family and its inhibitors (TIMPs) are a group responsible for extracellular matrix degradation and reconstruction. These enzymes are known to play important roles in tissue remodeling, morphogenesis, angiogenesis, and apoptosis.[18] Hipp et al. reported that the bladders of patients with myelomeningocele have excessive extracellular matrix deposition and inappropriate contraction, in addition, they are developmentally immature relative to healthy smooth muscle cells.[19] An upregulation of TIMPs is known to cause fibrosis by increased deposition of collagens to the bladder wall, along with an increase in interstitial cells including fibroblasts and myofibroblasts.[20] The loss of smooth muscle in the bladder tissues of children with myelodysplasia is compensated by the formation of type

3 collagen.[21] This situation causes deterioration of type 1/3 collagen ratio, storage of collagen in the extracellular matrix and increase in fibrosis. This process results in decreased bladder compliance, increased intravesical pressure and long-term renal injury. Inflammatory and fibroblastic responses also affect secretion of MMP in fibroblast.[22] Urinary TIMP-2 has been previously shown to be associated with elevated DLPP and UUT deterioration in children with spina bifida.[4] Peyronnet et al. reported that urinary MMP-2 is associated with low compliance in adult patients with spina bifida (0.72 ng/mL in patients with bladder compliance <20 cmH2O/mL vs. 0.48 ng/mL in patients with bladder compliance >20 cmH2O/mL).[6] In the same study, no significant relationship could be shown between MMP-2 and maximum detrusor pressure and MCC. In the present study, urinary MMP-2 was found to be significantly higher in children with myelodysplasia than in healthy children. However, no association between MMP-2 and compliance was found in the subgroup analysis. We found that urinary ATP was correlated with bladder compliance. Interestingly, although there was a positive correlation between ATP and MMP-2, no correlation was found between MMP-2 and bladder compliance (Table 3). We think that this result may be related to the small number of subjects in the study. Moreover, it should be kept in mind that although the relationship between these markers is statistically significant, it may not be clinically significant.

The last biomarker we studied, BDNF, is the second most common neurotrophic factor in the human body and plays an important role in neuroregeneration. BDNF supports cell differentiation and survival through the intracellular Ras—mitogen-activated protein kinase pathway.[23] Although increased BDNF may promote functional recovery, the effects of BDNF can break down sensory functions.[24] It has been shown that urinary BDNF is higher in children with nonneurogenic LUT dysfunction than in healthy children and decreases after treatment.[9] It has previously been evaluated in children with spina bifida in only one study. Although urinary BDNF values decreased after botulinum toxin injection, its relationship with urodynamic parameters could not be demonstrated.[5] Similarly, in another study involving adult patients with spina bifida, it was reported that there was no relationship between urinary BDNF values and urodynamic parameters such as bladder compliance, detrusor overactivity, maximum detrusor pressure, and maximum bladder capacity.[6] In the present study, urinary BDNF values were detected higher in children with myelodysplasia than in healthy children. However, as in MMP-2, its relationship with compliance was not observed.

In addition, our data showed that there was no relation between UUT deterioration and biomarkers (Table 2). Before this analysis, it was aimed to evaluate the biomarkers predicting groups at risk for UTT deterioration, not the direct process of damage. This may be due to the low number of patients. Moreover, the effect of CIC use, medical treatments, presence of UTI, and surgeries such as augmentation cystoplasty on urinary biomarker in children with myelodysplasia is unclear. Only urinary biomarkers and botulinum toxin relationship have been shown previously in children with myelodysplasia.[5,25] However, in these studies, no significant difference was found in subgroup analyzes according to urodynamic parameters. In the present study, 95% of the children were already using CIC, were receiving anticholinergic therapy, and there was no patient with augmentation cystoplasty. Therefore, the effect of these conditions on the urinary biomarker could not be evaluated. In our opinion, the ideal biomarker for LUT dysfunction should be easily measurable, reliable, sensitive, and specific to bladder functions, and predictive of treatment response. Although these results regarding biomarkers are promising, we think that the ideal biomarker specific to bladder dynamics is still far away.

This study has some limitations. The major limitation is the low number of patients for subgroup analyses. Since there were only five patients with bladder compliance >20 cmH2O, the cut-off value was defined as 10 cmH2O for statistical analyses. In addition, even if urinary ATP, MMP-2, and BDNF values were found to be different between the patient and healthy groups, we think that the lack of significant difference in subgroup analyzes may be related to the high number of patients with low bladder compliance. Although the ages were statistically similar between the patient and control groups, there was a wide age range. Studying these urinary biomarkers in selected age groups in the future may provide more reliable results. This was a case-controlled cross-sectional study. Posttreatment urinary biomarker values were not evaluated. Although video urodynamic examination was more appropriate in this patient group, it could not be performed due to lack of equipment. No evaluation was not made between urinary incontinence status and urinary biomarkers.

5 | CONCLUSION

Urinary ATP, MMP-2, and BDNF were found to be significantly higher in children with myelodysplasia than in healthy subjects. Moreover, a positive correlation was found between ATP and bladder compliance. They may

contribute to the follow-up of children with neurogenic LUTD in future with their noninvasive features. However, the lack of standardization, and the inability to reliably predict risky groups are important shortcomings of urinary biomarkers. We think that urine biomarkers still need to be evaluated for their ability to predict bladder dynamics in further well-designed studies.

AUTHOR CONTRIBUTIONS

Cagri Akin Sekerci: Concept-design; data interpretation; manuscript drafting and writing; statistical analysis; literature screening. **Mehmet Umut Kutukoglu**: Data acquisition. **Banu Isbilen Basok**: Biochemical analyses. **Mesut Fidan**: Biochemical analyses. **Sebahat Cam**: Data acquisition. **Selcuk Yucel**: Supervision. **Tufan Tarcan**: Concept-design, supervision.

ACKNOWLEDGMENTS

The study was financially supported by the Marmara University, School of Medicine Foundation.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

Ethical approval was obtained from the local ethics committee (Marmara University) before the study (No: 09.2021.250).

ORCID

Selcuk Yucel http://orcid.org/0000-0001-9837-5510
Tufan Tarcan http://orcid.org/0000-0002-3387-3524

REFERENCES

1. Tarcan T, Önol FF, İlker Y, Alpay H, Şimşĕk F, Özek M. The timing of primary neurosurgical repair significantly affects neurogenic bladder prognosis in children with myelomeningocele. *J Urol*. 2006;176(3):1161-1165.
2. Spinoit AF, Decalf V, Ragolle I, et al. Urodynamic studies in children: standardized transurethral video-urodynamic evaluation. *J Pediatr Urol*. 2016;12(1):67-68.
3. Koukourikis P, Papaioannou M, Papanikolaou D, Apostolidis A. Urine biomarkers in the management of adult neurogenic lower urinary tract dysfunction: a systematic review. *Diagnostics*. 2023;13(3):468.
4. Şekerci ÇA, Işbilen B, Işman F, Akbal C, Şimşek F, Tarcan T. Urinary NGF, TGF-β1, TIMP-2 and bladder wall thickness predict neurourological findings in children with myelodysplasia. *J Urol*. 2014;191(1):199-205.
5. Sekerci CA, Tanidir Y, Toprak T, et al. Value of urinary brain-derived neurotrophic factor levels on the assessment of botulinum toxin type A treatment for neurogenic detrusor overactivity in children with myelodysplasia. *J Urol*. 2019;201(1):174-181.
6. Peyronnet B, Richard C, Bendavid C, et al. Urinary TIMP-2 and MMP-2 are significantly associated with poor bladder compliance in adult patients with spina bifida. *Neurourol Urodyn*. 2019;38(8):2151-2158.
7. Silva-Ramos M, Silva I, Oliveira O, et al. Urinary ATP may be a dynamic biomarker of detrusor overactivity in women with overactive bladder syndrome. *PLoS One*. 2013;8(5):e64696.
8. Bauer SB, Nijman RJM, Drzewiecki BA, Sillen U, Hoebeke P. International children's continence society standardization report on urodynamic studies of the lower urinary tract in children: standardization of urodynamic studies in children. *Neurourol Urodyn*. 2015;34(7):640-647.
9. Özdemir K, Dinçel N, Berdeli A, Mir S. Can urinary nerve growth factor and brain-derived neurotrophic factor be used in the diagnosis and follow-up of voiding dysfunction in children? *Urol J*. 2016;13(3):2690-2696.
10. Sun Y, Keay S, De Deyne PG, Chai TC. Augmented stretch activated adenosine triphosphate release from bladder uroepithelial cells in patients with interstitial cystitis. *J Urol*. 2001;166(5):1951-1956.
11. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes-possible sensory mechanism? *J Physiol*. 1997;505(Pt 2):503-511.
12. Sadananda P, Shang F, Liu L, Mansfield K, Burcher E. Release of ATP from rat urinary bladder mucosa: role of acid, vanilloids and stretch. *Br J Pharmacol*. 2009;158(7):1655-1662.
13. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int*. 2004;45(7):987-993.
14. Birder LA, Barrick SR, Roppolo JR, et al. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. *Am J Physiol Renal Physiol*. 2003;285(3):F423-F429.
15. Smith CP, Vemulakonda VM, Kiss S, Boone TB, Somogyi GT. Enhanced ATP release from rat bladder urothelium during chronic bladder inflammation: effect of botulinum toxin A. *Neurochem Int*. 2005;47(4):291-297.
16. Cheng Y, Mansfield KJ, Allen W, Walsh CA, Burcher E, Moore KH. Does adenosine triphosphate released into voided urodynamic fluid contribute to urgency signaling in women with bladder dysfunction? *J Urol*. 2010;183(3):1082-1086.
17. Cheng Y, Mansfield KJ, Allen W, Millard RJ, Burcher E, Moore KH. Correlation between cystometric volumes, ATP release, and pH in women with overactive bladder versus controls. *Neurourol Urodyn*. 2013;32(7):969-973.
18. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*. 2003;92(8):827-839.
19. Hipp JA, Hipp JD, Yoo JJ, Atala A, Andersson KE. Microarray analysis of bladder smooth muscle from patients with myelomeningocele. *BJU Int*. 2008;102(6):741-746.
20. Fry CH, Kitney DG, Paniker J, Drake MJ, Kanai A, Andersson KE. Fibrosis and the bladder, implications for

function ICI-RS 2017. *Neurourol Urodyn*. 2018;37(S4): S7-S12.
21. Planta D, Gerwinn T, Salemi S, Horst M. Neurogenic lower urinary tract dysfunction in spinal dysraphism: morphological and molecular evidence in children. *Int J Mol Sci*. 2023;24(4): 3692.
22. Kim SJ, Kim J, Na YG, Kim KH. Irreversible bladder remodeling induced by fibrosis. *Int Neurourol J*. 2021; 25(suppl 1):S3-S7.
23. Segal RA. Selectivity in neurotrophin signaling: theme and variations. *Annu Rev Neurosci*. 2003;26:299-330.
24. Garraway SM, Huie JR. Spinal plasticity and behavior: BDNF-induced neuromodulation in uninjured and injured spinal cord. *Neural Plast*. 2016;2016:1-19.
25. Top T, Sekerci CA, Isbilen-Basok B, et al. The effect of intradetrusor botulinum neurotoxin type A on urinary NGF, TGF BETA-1, TIMP-2 levels in children with neurogenic detrusor overactivity due to myelodysplasia. *Neurourol Urodyn*. 2017;36(7):1896-1902.

How to cite this article: Sekerci CA, Kutukoglu MU, Basok BI, et al. The association of urinary BDNF, ATP, and MMP-2 with bladder compliance in children with myelodysplasia. *Neurourol Urodyn*. 2023;1-8. doi:10.1002/nau.25269