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URINARY HIGH-SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH NEUROGENIC BLADDER AFTER MENINGOMYELOCELE (MMC)

WYSOKO CZUŁE BIAŁKO C-REAKTYWNE W MOCZU PACJENTÓW Z PĘCHERZEM NEUROGENNYM PO OPERACJI PRZEPUKLINY OPONOWO-RDZENIOWEJ

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Summary

Introduction. Neurogenic bladder (NB) is specific condition caused by disturbed bladder innervation and the most often complication of meningomyelocele (MMC). It is known that incorrect bladder function causes renal damage. Condition of NB is worsened by urinary tract infections, detrusor overactivity, dysfunctional voiding and/or irregular catheterization. hs-CRP plays an important role in inflammatory process and can predict kidney function.

The aim of this study was the estimation of urinary hs-CRP level in association with neurogenic bladder function based on urodynamics and renal function based on eGFR in MMC patients with various activity states and with different levels of lesion.

Material and methods. 33 children and adolescents with urodynamically confirmed neurogenic bladder and 20 healthy individuals were enrolled into the study. Patients were divided according to Hoffer's scale and level of lesion. Urinary hs-CRP were evaluated in all individuals using ELISA methods. Urinary hs-CRP results were adjusted to the creatinine and expressed as hs-CRP/creatinine ratio. Nonparametric tests were used for statistical analysis.

Results. When compared to the reference group, MMC patients showed increased urinary hs-CRP. There were no differences in the studied parameter between boys and girls, non- and catheterized, and with different urodynamic diagnosed children. We found positive correlations between Hoffer's scale assessing physical activity and level of lesion and between GFR and urinary hs-CRP/crea.

Conclusion. Urinary hs-CRP level is elevated in MMC patients compared to reference group and could be considered as a very early marker of glomerular hyperfiltration.

Streszczenie

Wstęp. Pęcherz neurogenny jest to specyficzny stan spowodowany zaburzonym unerwieniem pęcherza i jest jednym z najczęstszych powikłań przepukliny oponowo rdzeniowej. Znany jest fakt uszkodzenia funkcji nerek w następstwie pęcherza neurogennego. Czynność pęcherza neurogennego pogarszana jest poprzez zakażenia układu moczowego, nadczynność wypieracza, dysfunkcyjną mikcję i/lub nieregularne cewnikowanie. Wysoko czułe białko C-reaktywne (hs-CRP) odgrywa istotną rolę w procesach zapalnych, jak również może być czynnikiem predykcyjnym funkcji nerek.

Celem pracy była ocena hsCRP w moczu w powiązaniu z czynnością pęcherza neurogennego ocenianą w badaniu urodynamicznym oraz funkcją nerek w oparciu o GFR u pacjentów z przepuklina oponowo-rdzeniową w zależności od aktywności fizycznej i poziomu uszkodzenia.

Materiał i metody. Do badania włączono 33 dzieci z potwierdzonym pęcherzem neurogennym i 20 zdrowych jako grupę referencyjną. Pacjenci zostali podzieleni zgodnie z poziomem uszkodzenia i ze skalą aktywności fizycznej Hoffera. Stężenie hs-CRP w moczu oceniono metodą ELISA

u wszystkich uczestników badania. Stężenie hs-CRP odniesiono do stężenia kreatyniny i przestawiono jako wskaźnik hs-CRP/kreatynina. Do analizy statystycznej użyto testów nieparametrycznych.

W y n i k i . U pacjentów z przepukliną oponowo-rdzeniową wykazano podwyższony hs-CRP w moczu w porównaniu do grupy kontrolnej. Nie było różnic w badanych parametrach pomiędzy chłopcami i dziewczynkami, pacjentami cewnikowanymi i nie cewnikowanymi, i pomiędzy pacjentami z różnymi rozpoznaniami urodynamicznymi. Wykazano pozytywne korelacje pomiędzy GFR i wskaźnikiem hsCRP/kreatynina a skalą Hoffera oceniającą aktywność fizyczną i poziomem uszkodzenia.

W n i o s e k . Stężenie hs-CRP w moczu jest podwyższone u pacjentów z pęcherzem neurogennym po przepuklinie oponowo rdzeniowej w porównaniu do dzieci zdrowych i może być rozważany jako wczesny marker hyperfiltracji.

Key words: neurogenic bladder, renal function, high sensitivity C-reactive protein, glomerular hyperfiltration
Słowa kluczowe: pęcherz neurogenny, czynność nerek, wysoko czułe białko C-reaktywne, hs-CRP, hiperfiltracja

INTRODUCTION

Neurogenic bladder (NB) is a specific, incurable condition caused by disturbed bladder innervation and most often follows meningomyelocele (MMC). It is well known that many factors, such as prostanoids, ATP, NO, cytokines, immunoglobulins, free oxygen radicals, nerve growth factor (NGF), are involved in normal bladder function and some of them affect NB functioning[1, 2, 3]. Improper bladder function also affects the appropriate function of kidneys tubules and glomeruli and, in consequence, causes renal function deterioration, and in many cases renal failure [4, 5]. The condition of NB is worsened by urinary tract infections (UTI), detrusor overactivity, dysfunctional voiding and/or irregular catheterization and the inflammatory process is a background of these abnormalities. High-sensitivity C-reactive protein (hs-CRP) is a very well-characterized marker of low-grade inflammation [6]. CRP determination in serum has been used to monitor anti-rejection therapy in patients after kidney transplantation and as a predictive diagnosis compared with kidney biopsy [7].

Kapelian et al. [8] have shown an association between overactive bladder (OAB) and lower urinary tract symptoms (LUTS) in men and women with elevated serum C-reactive protein levels. Chung et al. [9] reported that serum CRP levels were significantly higher in adults with OAB, interstitial cystitis (IC) and painful bladder syndrome (PBS) in both sexes but those levels were not as high as those in acute inflammation and can suggest that inflammation in bladder disorders was rather local and mild. In another study, Hsiao et al. [10] investigated serum CRP levels in women with LUTS and correlated them with parameters of urodynamics; they found higher CRP levels in patients with OAB than in those with low bladder capacity without urgency. Ferreira et al. [11] found both serum but not urinary levels higher in OAB patients compared with the controls. Considering the important role of hs-CRP in the inflammation process, increased urine level of this factor may affect NB function. However, the data estimating this effect and interrelations are not available in children populations, especially with neurogenic bladder due to MMC.

CRP levels can be measured in vaginal fluids and its high concentration is a marker of intra- amniotic inflammation/infection [12]. Urinary CRP levels were used in animal studies to measure glomerular dysfunction or kidney damage [13, 14]. High levels of CRP in serum can lead to elevated levels in urine, as CRP-is excreted in the urine [15]. Investigations in this field are limited, and it is interesting whether urinary CRP depends on glomeruli function. There are some difficulties with GFR estimation in NB patients. Firstly, evaluation based on the Counahan-Barratt equation carries the risk of error because of the difficulties in body length measurement caused by spine deformations. Secondly, clearance creatinine from 24-hour collection of urine can be false due to urine loss between catheterization. Therefore, serum creatinine and creatinine clearance determinations alone may not always correctly assess kidney function [16].

Hence, the aim of this study was to estimate of urinary hs-CRP levels in association with neurogenic bladder (based on urodynamics) and renal function in patients with NB after meningomyelocele in various activity conditions and different levels of lesion.

MATERIAL AND METHODS

Thirty-three children and adolescents aged median 8.17 (1.83-18) yrs (17 boys; 16 girls) with urodynamically confirmed diagnosis of NB after meningomyelocele were included in the study. Twenty healthy individuals (7 boys; 13girls, median age:11 (1-17) yrs) without a history of nephrological and

nervous system diseases (including UTIs) were enrolled as a reference (R) and they were recruited from healthy volunteers selected during examination before vaccination at the primary physician's office and from the hospital staff's children. The healthy subjects were on standard diet without any vitamins, drugs or diet supplements. Health status was determined based on the patients' medical past histories, parental reports, and routine laboratory tests to rule out the presence of acute and chronic inflammation.

Patients who met all the following inclusion criteria were enrolled in the study: 1. age: 1-18 years; 2. MMC patients with neurogenic bladder confirmed in cystometry; 3. normal blood pressure for age, centile of height and sex; 4. normal renal function (creatinine level in normal range, GFR>90ml/min/1.73m^2); 5. no clinical and laboratory signs of infection; 6. informed consent form signed by the patients and their parents. Patients with hypertension, UTI, diabetes mellitus, any other infections were excluded.

The non-catheterized NB patients and children from the reference group underwent uroflowmetry (3 times to increase test precision), and the averaged outcome was calculated. Most NB patients cannot empty their bladders by themselves so filling during cystometry was terminated when the infusion volume was the same as the patient obtains from everyday clean intermittent catheterization (CIC) because our intention was to imitate bladder function as in the natural environment. Additionally, urodynamic work-up included: in uroflowmetry: 1. time to max flow, 2. flow and voiding time, 3. maximum and average flow rate, 4. voided volume, 5. residual urine (calculated by USG immediately after micturition); in cystometry: 1. detrusor pressure at overactivity (Pdet overact), 2. intravesical pressure at maximum cystometric capacity (Pves CC), 3. bladder wall compliance (Comp), electromiography (EMG) of sphincter at the beginning (EMG 1) and at the end (EMG 2) of the filling phase. Urodynamic-based diagnoses were classified as: neurogenic detrusor overactivity (NDO), areflexic bladder (AB), neurogenic detrusor-sphincter discoordination (NDSD).

Patients were divided into 4 groups according to Hoffer's scale (HS), which assesses physical activity (1HS- wheelchair-dependent patients, 2HS – therapeutic walkers, 3HS – household walkers, 4HS – community walkers). Moreover, patients were divided according to the level of lesion based on the neurosurgical data into three groups: 1-thoraco-lumbar (Th-L), 2- lumbar-sacral (L-S), 3- sacral (S).

The age, sex, height, weight, body mass index (BMI), blood pressure (BP) and underlying comorbidities were recorded.

The first daytime urine samples were collected from all examined participants and stored at -80^{o}C for further analysis. Urine hs-CRP levels were measured by ELISA according to the manufacturer's instructions (Immundiagnostik AG, Germany), and then adjusted for urine creatinine concentration and expressed as hs-CRP/creat ratio (ng/mg creatinine). The biochemical work-up included: in urine: UA excretion (g/24h), creatinine concentration and urine osmolality; in serum: concentration of creatinine (measured by Jaffe reaction), urea and UA. Urinalysis was performed to exclude subjects with hematuria and leukocyturia. The glomerular filtration rate (GFR) was calculated using the Counahan-Barratt Equation (eGFR): GFR = 0.43 x L (cm)/ Scr (mg/dl), L – length, Scr – serum creatinine level [17]. Glomerular hyperfiltration (GHF) was defined as eGFR>140ml/min [18].

All the participants' demographic and biochemical data were statistically analyzed and expressed as median with minimum and maximum. The Mann-Whitney U test was used for comparisons between patients and the control group. The Spearman test was used to calculate correlations between the studied parameters. All statistical analyses were performed using Statistica 10.0. A p-value of less than 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Medical University of Bialystok in accordance with the Declaration of Helsinki.

RESULTS

The clinical and biochemical characteristics of the study participants and comparisons between the two groups are listed in Table 1.

Overall median age of all children with MMC was 8.17 (1.83-18) years. The age, sex and BMI of the studied children did not differ from the reference group (p=0.18; p=0.25; p=0.65, respectively). We found statistically significant differences in the parameters of physical development (body weight p=0.01 and height p<0.001), which is a result of the main disease. The MMC children demonstrated lower muscle mass (due to limbs paralysis) or excess body weight resulting from a lack of physical activity (wheelchair-bound).

Moreover, differences in body length were caused by distortions and malformations of the bone structure.

Table I. *The median values and ranges of basic demographical data and examined parameters in MMC children and reference group. Comparisons between both studied groups. Significant value: *p< 0.05; **p<0.01*

Tabela I. *Wartości mediany i zakresy podstawowych danych demograficznych i badanych parametrów u pacjentów z przepukliną oponowo-rdzeniową i w grupie referencyjnej. Porównania pomiędzy obiema badanymi grupami. Istotność statystyczna: *p< 0.05; **p<0.01*

Parameters (SI)/Parametry	MMC N=33	Reference N=20	Comparison p
	Median (minimum-maximum)		
F/M	16/17	13/7	0.25
Age/Wiek (years/lata)	8.17 (1.83-18)	11 (1-17)	0.11
Height/Wzrost (cm)	1.2 (0.81-1.67)	1.54 (0.76-1.9)	<0.001*
Weight/Masa ciała (kg)	28 (6.87-92)	38.5 (8.1-71)	0.01*
BMI (kg/m^2)	15.91 (9.08-37.19)	18.08 (12.02-24.51)	0.65
S creatinine (mg/dl)	0.31 (0.18-0.77)	0.51 (0.2-0.85)	<0.001*
S urea (mg/dl)	27 (11-42)	31 (16-40)	0.48
S UA (mg/dl)	3.86 (1.32-7.33)	3.94 (3.35-5.25)	0.74
U creatinine (mg/dL)	51.65 (15.84-111.54)	129.55 (63.56-244.05)	<0.001
U UA (g/24h)	0.3 (0.13-0.91)	0.34 (0.1-0.52)	0.35
eGFR (ml/min/1.73m^2)	180.1 (93.26-310)	134.16 (110-240)	0.06
Osmolality (mOsm/kgH_2O)	711.5 (357-1177)	690 (391-1200)	0.67
24h urine collection (ml)	660 (100-1500)	925 (400-1500)	0.21
hs-CRP/crea (ng/mg creatinine)	8.52 (3.32-23.58)	3.72 (1.53-12.66)	<0.001

MMC – meningomyelocele patients/pacjenci z przepukliną oponowo-rdzeniową, F/M – Female/Male; Dziewczynki/Chłopcy, S – serum/surowica, U – urine/mocz, UA – urine acid/kwas moczowy, e-GFR – Counahan- Barratt Equation

When compared to the reference group, MMC patients showed increased urinary hs-CRP (p<0.001) (Figure 1). Elevated urinary hs-CRP/crea was found in MMC patient with GHF (median 9.88 (3.32-23.58) compared with MMC patients with normal GFR (median 6.2 (3.33-8.68)(p=0.005). There were no differences in the studied parameter between boys and girls (p=0.68), and between non- and catheterized children (p=0.22). When we compared the studied participants between the HS groups according to physical activity, we found statistically significant differences in urinary hs-CRP/crea (Chi^2=15.44; p=0.002) (Figure 2). There were no differences in urinary hs-CRP/crea between patients with different urodynamic diagnoses (Chi^2=4.74; p=0.19). We did not find any correlations between urinary hs-CRP/crea and all uroflowmetry and cystometry urodyanamics parameters. The patients differed in GFR according to lesion level (Chi^2= 9.92; p=0.007) and in Hoffer's scale (Chi^2=7.82; p=0.049). Higher GFR was in patients with Th-L lesion level and in the 1HS group (wheelchair-dependent patients), and the lower GFR level was in patients with S lesion and in the 4HS group. Detailed data are shown in table II.

Table II. *Urinary hs-CRP and GFR in patients with MMC depending on the level of lesion and Hoffer's scale (HS). 1HS – wheelchair dependent patient, 2HS – moving with difficulties, 3HS – need support during moving, 4HS – moving without problems*

Tabela II. *hs-CRP w moczu i GFR u pacjentów z przepukliną oponowo-rdzeniową w zależności od poziomu uszkodzenia i skali Hoffera (HS). 1HS – pacjent poruszający się na wózku, 2HS – poruszający się z dużymi problemami, 3HS – wymagający niewielkiej pomocy podczas poruszania się, 4HS – poruszający się bez żadnych ograniczeń*

	TH-L	L-S	S	1HS	2HS	3HS	4HS
	Median (minimum-maximum)						
Urinary hs-CRP/crea hs-CRP/ kreatyniny w moczu	10.4 (3.3-16.8)	8. (4.-23.6)	6.2 (3.3-11.9)	9.2 (3.3-23.6)	10.8 (7.2-21.8)	8. (4.-9.9)	6.3 (3.3-11.9)
eGFR ml/min/1.73m^2	197.5 (155.9-310)	148.5 (93.3-263.9)	128.7 (103.9-180.1)	193.5 (93.3-310)	172 (111.6-215)	191.1 (140.9-215)	149.8 (103.9-330)

We found a positive correlation between Hoffer's scale assessing physical activity and lesion level (r=0.69; p< 0.05), GFR (r=-0.28;p<0.05) and urinary hs-CRP/crea (r=-0.554, p<0.05). Serum creatinine correlates positively with serum UA (r=0.482, p<0.05) and urine creatinine level (r=0.475, p<0.05), and negatively with GFR (r=-0.865, p<0.05) in MMC patients. GFR correlates negatively with physical development parameters such as: age (r=-0.476, p<0.05), height (r=-0.459, p<0.05) and weight (r=-0.355, p<0.05) but not with BMI (r=-0.147, p>0.05). There were no such correlations in the reference group. The correlations between urine hs-CRP/crea and

height, serum creatinine and GFR in children with NB are shown in Figure 3. We did not find such correlations in the reference group. We revealed positive correlation between urine osmolality and hs-CRP (ng/ml)(r=0.399, p<0.05) and negative between urine osmolality and hsCRP-(ng/g creat)(r=-0.129, p>0.05).

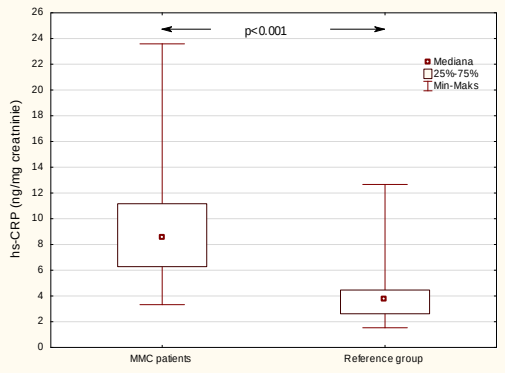

Fig. 1. *Urinary hs-CRP in patients with MMC and reference group*

Ryc. 1. *hs-CRP w moczu pacjentów z przepukliną oponowo-rdzeniową i w grupie referencyjnej*

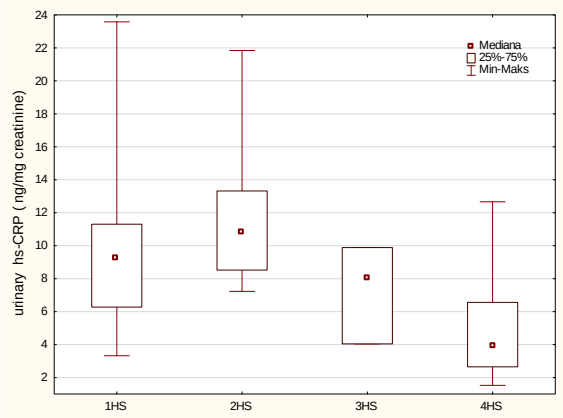

Fig. 2. *Urinary hs-CRP in MMC patients in various physical activity stages. 1HS- wheelchair dependent patient, 2HS - moving with difficulties, 3HS - need support during moving, 4HS - moving without problems*

Ryc. 2. *hs-CRP w moczu pacjentów z przepukliną oponowo-rdzeniową w różnych stanach aktywności fizycznej. 1HS- pacjent poruszający się na wózku, 2HS – poruszający się z dużymi problemami, 3HS – wymagający niewielkiej pomocy podczas poruszania się, 4HS – poruszający się bez żadnych ograniczeń*

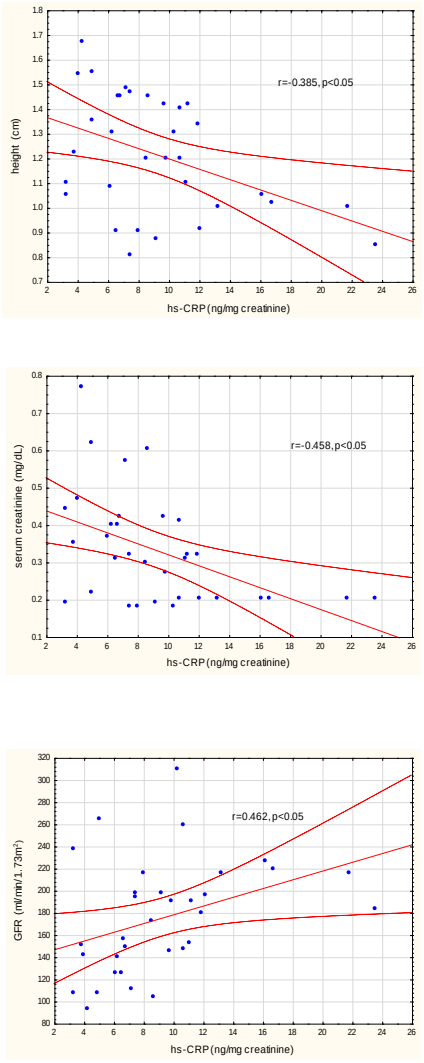

Fig. 3. *Correlations between urine hs-CRP and height, serum creatinine and GFR in MMC patients*

Ryc. 3. *Korelacje pomiędzy hs-CRP a wzrostem, poziomem kreatyniny i GFR u pacjentów z przepukliną oponowo-rdzeniową*

DISCUSSION

Elevated hs-CRP levels in patients with disturbed bladder function have been considered in many studies [8, 9, 11]. Additionally, Hsiao et al. [10] revealed that increased serum CRP was correlated with a low maximum flow rate, suggesting that patients with a low maximum flow rate had bladder dysfunction secondary to inflammation in detrusor muscles or bladder outlet obstruction. Decreased serum CRP after systemic inflammation therapy suggests that CRP might be a useful biomarker for monitoring disease status and for treatment response in patients with LUTS. We cannot confirm this observation based on our study. All

patients had normal serum CRP. They differed in urinary hs-CRP compared with the reference group. Estimation of hs-CRP in respect to bladder function in fairly homogenous group of patients (neurogenic bladder caused by abnormal innervation due to meningomyelocele) did not show any correlations between urinary hs-CRP and cystometry and uroflowmetry parameters. On the other hand, the lack of correlations with uroflowmetry parameters can be the result of the small group of patients on whom this procedure has been performed. Ferreira et al. [11] found both serum and urine levels elevated in adult patients with overactive bladder (OAB). OAB is not a urodynamic term, but means a clinical condition where urgency is a subjective hallmark and patients with this symptom can be said to have OAB. In this study, the patient group was not uniform and CRP estimation in this group was not very precise. We did not find any differences in urinary hs-CRP between patients with and without NDO proved by urodynamics, and also between other urodynamics diagnoses (AB and NDSD). We think that estimation of urinary CRP could be more credible, because of false positive results of increased serum CRP level as a result of obesity, diet or other comorbid conditions [19].

Elevated hs-CRP levels in MMC patients have another explanation. As a very early marker of inflammation, it can suggest that there are some factors which can cause inflammation in neurogenic bladder especially in the absence of the evident features of infection. It is well known that oxidative status is disturbed in MMC children, the level of NGF was elevated and that a correlation between hs-CRP and NGF was revealed in patients with lower urinary tract dysfunctions [20, 21, 22, 23]. Those studies were based on patients without neurogenic impairments. We compared urinary hs-CRP levels between catheterized and non-catheterized patients and did not find any differences between these two groups. We suspect that irritation of the bladder during catheterization or bladder distention in not catheterized children can provoke inflammation and it is the reason for elevated urinary hs-CRP in both groups without any differences between them. Moreover, the small group of non-catheterized children can affect the findings and further studies are necessary to distinguish between these two groups.

As it is well known, it is possible to expect elevated urinary levels in urine due to high serum levels as the CRP is excreted in urine. Urinary hs-CRP was measured in animal studies and was connected with proteinuria observed in different stages of renal damage with elevated serum creatinine [13, 14]. Our patients had serum creatinine in the normal range, even statistically significant lower than in the reference group. It is very probable that these findings are due to glomerular hyperfiltration (GHF), which in fact we confirmed in our MMC patients. Hence, increased urinary hs-CRP can be followed by hyperfiltration. A positive correlation between urinary hs-CRP and GFR and a statistically significant higher level in patients with GHF indicate that urinary hs-CRP could be used as a very early marker of renal dysfunction, especially in such an incurable state as NB. It is also proven that estimation of GFR in patients with MMC and bladder neurogenic dysfunction is subject to error because of the reasons mentioned above (disproportion in body features and loss of urine between everyday catheterizations). Low serum creatinine concentrations can be caused by GHF, and it is very important to remember that correct estimation of GFR and proper interpretation of serum creatinine concentrations in patients with MMC protect against renal function deterioration and enable us to improve MMC follow-up.

Additionally, we revealed that GFR negatively correlates with different activity states and lesion level in MMC patients. Wheelchair-dependent patients and those with L-S lesion level presented the highest GFR and all had GHP. Thus, they need a special approach and perfect estimation of renal function as it is well known that GHF is considered an early marker of renal damage and that albuminuria positively correlates with markers of inflammation [24, 25].

In summary, we are convinced that profound knowledge about factors that increase risk is a standard way to guide prevention and very early intervention. That is why we are looking for new, simple markers which might be useful in the qualification of MMC patients into the group of increased risk for secondary kidney damage.

We realize that our study had some limitations. Firstly, the group of patients was not very numerous. Secondly, we suspect that the lack of correlations between urinary hs-CRP and urodynamic diagnoses could be caused by the pharmacological treatment which was applied to the most of the studied patients. Additionally, we think that urinary hs-CRP estimation in connection with other biomarkers of LUT dysfunction could be more valuable as an

inflammatory process predictor. It is worth planning another study on a more numerous population with factors which accurately estimate renal function, e.g. cystatin C, and correlate it with urinary hs-CRP levels for confirmation of the role of hs-CRP in assessing very early renal function deterioration. Finally, we cannot exclude that some of the higher hs-CRP levels were explained by subclinical infection, although all participants had negative serum CRP levels. We also wonder whether and/or which factors could stimulate the inflammatory process in neurogenic patients without any signs and symptoms of infections. More studies are needed to clarify these relations.

Conclusion/Wniosek

Urinary hs-CRP level is elevated in MMC patients compared with the reference group and could be considered a very early marker of GHF.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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