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Clinical characteristics of patients with neurogenic bladder due to myelomeningocele – Eighteen-year retrospective study; University Children's Hospital, Bialystok, Poland

Kliniczna charakterystyka dzieci z pęcherzem neurogennym po operacji przepukliny oponowo rdzeniowej – 18 lat retrospektywnych badań; Uniwersytecki Dziecięcy Szpital Kliniczny, Białystok, Polska

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ABSTRACT

Introduction: Myelomeningocele (MMC) is congenital nervous system malformation caused by neurulation process failure during pregnancy. The prevalence varies by the continent, region, race, ethnicity and the time when assessed and patients present abnormalities of different organs. One of the most severe complications is renal failure. **Aim:** Clinical evaluation of patients with MMC in North-East Poland and answering the question whether our treatment methods lead to renal function preservation. **Material and methods:** Medical records of 112 patients in the period 1995–2013 were evaluated retrospectively.

The data included: age, sex, BMI Z-score WHO, place of residence, perinatal history, social situation, physical activity, urodynamic diagnosis, renal function, hydrocephalus diagnosis, and functioning of shunting procedures. **Results:** They were no statistically significant differences in most studied parameters between boys and girls. We observed statistically significant differences among MMC patients divided into 4 groups according

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Słowa kluczowe:
- przepuklina oponowo-rdzeniowa
- badania epidemiologiczne
- pęcherz neurogenny
- czynność nerek
- aktywność fizyczna

to the physical activity. They differed in birth weight and length, Apgar scale, hydrocephalus diagnosed and the need for ventriculoperitoneal shunt. We did not find differences in urodynamic diagnosis among 4 studied groups. **Conclusions:**

1. Data of MMC children from Poland are similar to the other countries.
2. In our opinion, early diagnostic and treatment procedure especially with early catheterization of MMC children prevent renal failure development.
3. Assessment of very early markers in renal function deterioration in neurogenic bladder patients from widespread multicenters' research is indicated.

Introduction

Myelomeningocele (MMC) is congenital malformation of the central nervous system caused by the failure of the neurulation process during early pregnancy. The prevalence of MMC varies by the continent, region, race, ethnicity, and evaluated period and the rate is between 2.8 and 19.6:10 000 [1–5]. The incidents of MMC for the past 10 years have been decreasing and such a trend is an effect of early detection and termination of the pregnancy [6–8]. Folates administration in women is one of the reasons for decreasing incidence of MMC [9, 10]. Patients with MMC present many abnormalities and the most affected systems are nervous, skeletal and urinary. Lifelong, many specialist follow-ups should be focused on improving and/or keeping the correct function of these organs and systems. Our prevention and treatment should not only lead on to extending the life but also improve the quality of life.

The aim of this study was clinical evaluation of MMC patients in Podlasie province from January, 1995 to December, 2013 at the University Children's Hospital (UCH) in Bialystok. It was our intention to evaluate the origin of MMC children, family structures, course of the pregnancy and childbirth, function of the urinary tract and mutual correlations. We also would like to answer the question and assess if our very detailed diagnostic process and meticulous follow-up were appropriate and lead to preserving renal function in MMC patients when they are susceptible to progressive renal damage.

Material and methods

Medical records of 112 patients have been drawn from a computerized database and were evaluated retrospectively. The data included: age, sex, place of residence, perinatal history, social situation (living with parents, in foster family or nursing house), physical activity assessed using Hoffer's scale, urodynamic diagnosis, presence of the hydrocephalus, requirement of shunting procedures (ventriculoperitoneal shunt – VPS), and number and kind of clinics which they have been attending.

The physical activity of each case was graded using Hoffer's scale (1HS – wheelchair-depended patient, 2HS – moving with difficulties, 3HS – need support during moving, 4HS – moving with any problems) [11]. Urodynamic findings were classified based on the estimation of detrusor pressure, sphincter activity and bladder wall compliance as: neurogenic detrusor overactivity (NDO), areflexic bladder (AB), neurogenic detrusor-sphincter discoordination (NDSD), poor bladder wall compliance (PBC) and normal bladder function (NBF).

MMC patients have been also divided based on the neurosurgical data according to lesion region into 3 groups: 1-thoracolumbar (Th-L), 2 – lumbar-sacral (L-S), and 3 – sacral (S). We have also provided some demographic data from Podlasie province – place of our patients' origin – and divided the follow-up period into 2 parts: I – last 10 years; II – earlier years.

Renal function based on the serum creatinine and eGFR by the Counahan–Barratt equation [12] were estimated twice: first when admitted to UCH and at the last when the patient was presented; they were studied in 4 age groups: I – <3 years, II – 4–6 years, III – 7–15 years and IV – >15 years old. BMI Z-score WHO was calculated in all the enrolled study patients on the time of their last stay at USK. In order to evaluate physical development we arbitrarily classified into grade as follow: -2 >normal <2, overweight >2 and underweight <-2 [13].

The data were collected in Microsoft Excel database. Statistical analysis was performed using Statistica 10.0. Values were given as medians, frequencies or percentages. Nonparametric data were evaluated with the ANOVA analysis and Wilcoxon and Mann–Whitney tests. Correlations were assessed by Spearman test. p value less than 0,05 was accepted as statistically significant.

Patients and their parents were enrolled in the study after obtaining informed consent. The study protocol was approved by the Ethics Committee, Medical University of Bialystok and was conducted in accordance with the Declaration of Helsinki.

Results

During the study period, 120 patients were admitted because of MMC, 8 refused participation and remaining 112 patients formed the study group. Six patients were seen only one time and then were lost during our follow-up. Three girls aged 5, 7 and 17 years died during the observed period. The cause of death was general infection and dialysis complications. A part of these patients were seen at the illness onset and mostly they were admitted to our hospital later.

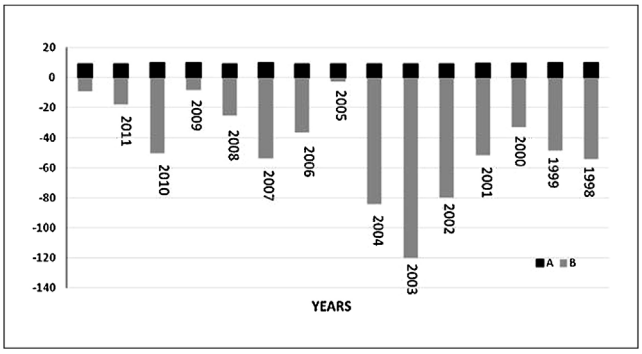

Fig. 1 – Number of newborns per 1000 population (A) *versus* number of MMC newborns per 100 000 population (B) in Podlasie province (North-East part of Poland)
The data comes from Statistical Central Office reports in the period 1998–2012 [27]

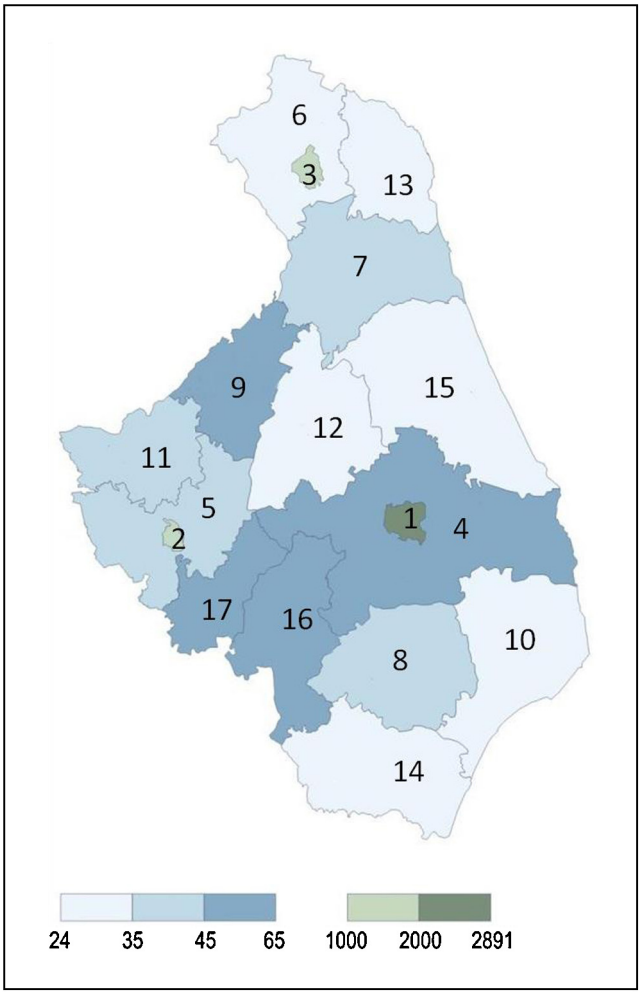

Fig. 2 – Population density in 17 consecutive districts of Podlasie province
The data comes from Statistical Central Office report 2012 [27]

In the 1993–2003 period 64 and in the 2004–2014 period 48 patients were born with MMC. Detailed data about healthy children and patients with MMC are shown in Fig. 1. The patients' origin is shown in Fig. 2. As it appears from this graph there is one district with no MMC patient (north part of Podlasie), next to the Lithuania border where 30% of the population has Lithuanian origin. The most MMC children per 100 000 population live in Łomża city and in district nr 16. The detailed demographic data are shown in the Table I. Most MMC children were parented by a complete family (96/112, 85.71%). Only 2 patients (2/112, 1.79%) were living with their mother and 1 boy (1/112, 0,89%) with his father. Four children stayed in an education institution (4/112, 3.57%) and 3/112 (2.67%) lived with a foster family.

The detailed antenatal and postnatal characteristics of analyzed patients divided in physical activity groups are shown in Table II. The median age of MMC patients was 9.13 (0.33–18) years. The median weight was 26.8 (6.45–89) kg and length was 120 (58–177) cm. There were no differences in these parameters between girls and boys ($p = 0.165$; $p = 0.054$ respectively). The patients were estimated twice: I – in the beginning of follow-up (at first admission to UCH) and II – on the patient's last stay at UCH. The median age of MMC patients during first estimated time was 1.40 (0.10–16.00) years and the median time of observation was 5.53 (0.1–16.33) years. We found statistically significant differences in birth weight ($p = 0.03$) and length ($p = 0.02$) among studied patients according to the Hoffer's scale. The most children were born from the first pregnancy, 38/92 (41.30%). From the second were born 27/92 (29.34%), from the third pregnancy 10/92 (10.87%), from the fourth pregnancy 9/92 (9.78) and from the fifth and more were born 8/92 (8.7%). Miscarriages were declared by10/92 (10.87%) mothers; in 2 women twice and in one case a child with anencephalia was born. We found statistically significant differences in Apgar scale among the studied group ($p = 0.01$). There were no differences in gestational age ($p = 0.85$) and place of the living ($p = 0.065$) between the 4 Hoffer's scale groups. Hydrocephalus was diagnosed in 86.1% of MMC and we found differences between the groups ($p < 0.001$). 89% of the patients with hydrocephalus required ventriculoperitoneal shunt (VPS) and the differences between groups were significant ($p < 0.001$).

VURs were diagnosed in 32.58% individuals and there were no differences between groups ($p = 0.08$). The VUR I° was diagnosed in 24.14%, II° in 27.59%, III° in 17.24%, IV° in 13.79% and V° in 17.24% of MMC patients.

A further analysis was conducted according to the first urodynamic diagnosis in 92 patients. Only one child (1.09%) had NBF during all follow-up periods. NDO were diagnosed in 57.61% patients. Eight (8.7%) patients were diagnosed with AB and 10.87% with NDSD. PBC had 21.74% MMC patients. Tethered Cord Syndrome (TCS) developed in 13.04% patients.

The catheterization was necessary in majority of the MMC patients. We estimated it during the last patient's stay at UCH and there were no differences between the groups ($p = 0.08$).

MMC patients were attending the median 7 (1–18) outpatient clinics, and there were no differences between the

Table I – Demographic data of Podlasie province, North-East part of Poland

	MMC (people/100 000 population)	Population density (people/km^2)	Total district population	District area (km^2)
1	6.1	2882	294 925	102.12
2	31.97	1921	6275	32.67
3	8.65	1060	69 331	65.24
4	11.82	48.2	143 864	2984.64
5	9.58	38.55	52 196	1353.93
6	8.31	27.6	36 120	1307.31
7	5.01	36.1	59 914	1658.27
8	8.59	42.03	58 225	1385.2
9	14.19	51	49 327	967.24
10	6.48	28.53	46 327	1623.65
11	7.52	42.46	39 903	939.73
12	7.04	30.74	42 606	1385.39
13	0	24.17	20 969	856.07
14	8.4	32.62	47 611	1459.58
15	12.6	37.67	71 411	2055
16	18.55	46.02	59 313	1288.91
17	2.2	61.37	44 990	733.11

The data comes from Central Statistical Office report, 2013 [27]. 1–17 – districts of Podlasie Province

Table II – The antenatal and postnatal characteristics of MMC patients

	All patients	HS 1	HS 2	HS 3	HS 4
	N – number of patients; median (minimum = maximum) or (percentage within the group)				
Female/male	112; 60/52	55; 31/24	17; 7/10	12; 9/3	16; 8/8
Birth weight (kg)	92; 3.145 (1.2–4.8)	55; 3.1 (1.68–4.8)	14; 3.04 (1.2–3.95)	10; 3.33 (2.3–4.3)	13; 3.2 (2.9–4.2)
Birth length (cm)	84; 54 (40–61)	55; 52 (40–58)	7; 55 (49–58)	9; 53.5 (50–61)	13; 55 (52–61)
Type of delivery cesarean/vaginal	81; 47/34	44; 26/18	14; 11/3	11; 5/6	12; 5/7
Complicated pregnancy (%)	81; 18 (22.2)	44; 7 (15.91)	14; 6 (42.86)	11; 3 (27.27)	12; 2 (16.67)
Gestational age (weeks)	78; 40 (32–43)	43; 40 (32–42)	13; 38 (33–43)	10; 40 (35–41)	12; 40 (33–41)
Apgar scale	81; 8 (1–10)	43; 8 (1–10)	14; 8 (1–10)	11; 8 (6–10)	13; 9 (6–10)
Domicile (T/V)	100; 60/50	55; 25/30	17; 14/3	12; 6/6	16; 9/7
Hydrocephalus (%)	95; 82 (86.31)	55; 46 (83.64)	16; 14 (87.5)	9; 3 (33.33)	15; 6 (40.0)
VPS (%)	95; 59 (62.11)	55; 42 (76.36)	16; 12 (75)	9; 2 (22.22)	15; 3 (20)
VUR (%)	89; 29 (32.58)	50; 21 (38.17)	16; 3 (17.64)	11; 4 (33.33)	12; 1 (6.25)
Catheterization (%)	97; 62 (63.92)	53; 40 (75.47)	17; 9 (52.94)	12; 6 (50)	15; 7 (46.67)
Number of clinics	99; 7 (1–18)	55; 7 (1–18)	17; 7 (1–12)	12;7.5 (2–12)	15; 7 (4–12)
BMI	94; 17.9 (9.6–37.2)	55; 17.4 (9.6–37.2)	14; 20.2 (12.3–31.5)	11; 19.2 (11.8–29.3)	14; 16.7 (13.1–22.4)
BMI Z-score WHO	92; 0,45 (−7.31 to 4.26)	53; 0,59 (−7.31 to 2.26)	14; 1.41 (−2.97 to 2.97)	11; 0,91 (−3.48 to 2.65)	14; −0.07 (−2.48 to 2.8)

HS, Hoffer's scale; T, town; V, village; VPS, ventriculoperitoneal shunt; VUR, vesico-ureteral reflux; BMI, body mass index.

4 studied groups. Patients were attending 37 different clinics. Detailed data are shown in the Fig. 3.

The median BMI Z-score WHO was 0,446 (−7.307 to 4.255). There were no differences in BMI Z-score WHO between boys and girls ($p = 0.184$, $p = 0.105$ respectively). We did not find any differences in BMI Z-score WHO among patients in Hoffer's scale ($p = 0.3$) and between 2 estimated periods ($p = 0.46$), home place ($p = 0.45$), patients with hydrocephalus ($p = 0.7$), and type of delivery ($p = 0.54$). Among overweight patients 3.03% were obese and among underweight 5.05% were severe underweight.

The most frequent level of lesion was L–S in 51.79% and the most rare was S localization (7.14%). Th-L has been reported in 32.14% of the individuals. We found positive

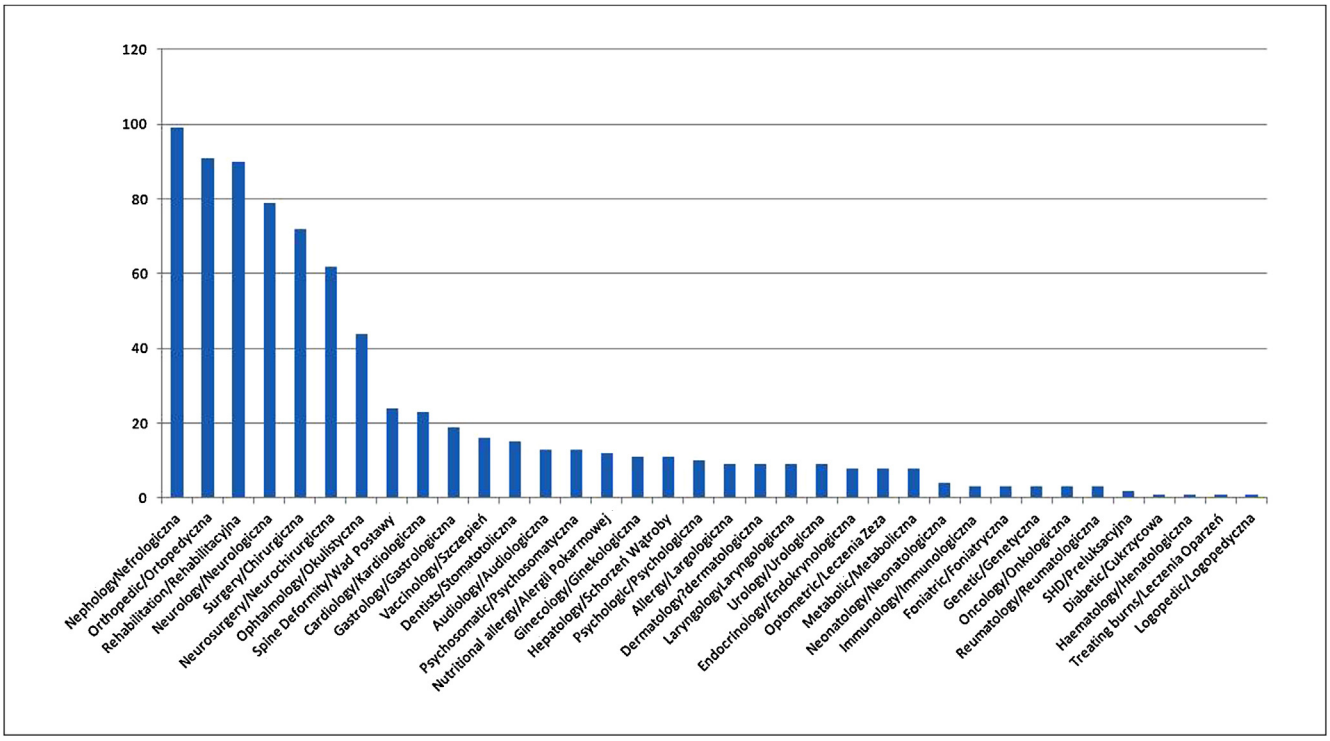

Fig. 3 – Number of children attending to the specialist clinics in the course of 15-year follow-up. SHD – Screening of Hip Dysplasia

Table III – Laboratory characteristics of MMC children. S creatinine – serum creatinine. I – data from the first estimation. II – data from the last estimation, eGFR – glomerular filtration rate estimated by Counahan–Barratt equation

	All patients	<3 years $n = 17$	3–6 years $n = 24$	7–15 years $n = 50$	>15 years old $n = 21$
		Median (minimum–maximum)			
S creatinine I (mg%)	0.27 (0.11–2.49)	0.23 (0.18–0.40)	0.2 (0.16–0.51)	0.27 (0.11–2.49)	0.41 (0.23–0.77)
S creatinine II (mg%)	0.31 (0.18–8.57)	0.23 (0.18–0.31)	0.21 (0.18–0.63)	0.34 (0.18–8.57)	0.57 (0.32–1.03)
Uric acid I (mg%)	3.78 (1.29–18.03)	3.8 (2.09–5.57)	3.25 (2.29–4.25)	3.83 (1.29–8.48)	4 (2.04–6.22)
Uric acid II (mg%)	4.08 (2–9.43)	3.65 (2.00–4.91)	3.95 (2.69–5.25)	4.04 (2.08–9.43)	4.8 (3.74–7.66)
Urea I (mg%)	23.00 (7.00–98.00)	20.00 (7.00–43.00)	21.00 (8.00–57.00)	23.40 (10.00–98.00)	27.00 (10.00–38.00)
Urea II (mg%)	27.00 (12.00–212.00)	26.50 (12.00–35.00)	29.00 (19.00–40.00)	27.00 (16.00–212.00)	25.50 (10.00–40.00)
eGFR (ml/min/1.73/m^2)	161.25 (4.77–313.92)	160.78 (110.97–193.51)	199.64 (64.84–249.40)	168.92 (4.77–313.90)	114.22 (71.39–204.25)
Urine osmolality	693.5 (274–1177)	574 (280–873)	696 (316–931)	732.5 (274–1177)	655 (382–960)

correlation between level of lesion and physical activity ($r = 0.696$; $p < 0,05$), between hydrocephalus and VPS with Hoffer's scale ($r = 0.391$, $r = 0.434$ respectively; $p < 0.05$) and with level of lesion ($r = 0.288$; $r = 0.401$ respectively; $p < 0.05$). We did not find correlation between level of lesion and sex ($r = -0.068$, $p > 0.05$). Apgar scale correlated positively with Hoffer's scale ($r = 0.271$, $r = 0.284$ respectively; $p < 0.05$) and eGFR correlated negatively with the level of lesion ($r = -0.2925$, $r = -0.25954$; $p < 0.05$).

Renal function deterioration was found in 10.87% patients. Detailed laboratory data of MMC children in respect of age are included in Table III. We found differences between creatinine I and II ($p = 0.004$), urea I and urea II ($p = 0.003$) and uric acid I and II ($p = 0.01$) in MMC children. We also found differences in creatinine I, creatinine II and eGFR among patients in the 4 age groups ($p < 0.001$, $p < 0.001$ and $p = 0.008$ respectively). We did not find any differences in median urinary osmolality within the groups ($p = 0.62$).

Discussion

Studies in this part of Europe are limited. To the best our knowledge it was the first large and long-time study in North-East part of Poland. Au et al. [14] described that lesion levels located on/above L1were more frequent in female patients. In our study, female patients are more frequent in HS1 group but did not correlate with lesion region. Results of our analysis about hydrocephalus, need of VPS procedure and TCS complication are similar to Talamonti et al. [15] study where most patients had enlarged ventricles but only

78% needed VPS and 20% patients presented TCS and also to a Swedish study performed by Olsson et al. [16] where hydrocephalus was seen in 86% and 31% needed surgery because of TCS. We can speculate that the natural history of MMC is similar despite differences in patients between countries, ethnicities and races.

We used BMI Z-score WHO for assessing physical condition of our patients. We realize, that up to now, we do not have a perfect tool for the measurement of physical feature as body length in patients with scoliosis or deformation of lower limbs. We took all dimensions of our patients in the same, lying position. Overweight/obesity are growing problems in children of developed countries and our study confirms that this problem is also in regard with MMC individuals.

Roach et al. [17] demonstrated that 100% patients with thoracic level and 86% with L1–L3 were full-time wheelchair-dependent and 100% with sacral localization walk without any support. In our study level of lesion correlates positively with activity and 100% of the patients with TH-L lesion were in 1HS scale but 12.5% patients with S level of lesion were classified as 3HS.

The cause of death in our patients was the same as in other studies: general infection and renal failure [17, 18]. Two girls who died during the observed period were admitted to UCH in the end stage of renal failure. Both the girls' parents did not respect bladder catheterization recommendations. It is worth to underline that VURs, areflexic bladder and incompetent urethral function were diagnosed in both of them. As it was stated in Roach et al. [17] study the mortality of MMC patients was very high more than fifty years ago and was about 20% in patients aged 31 years. Fortunately, the mortality decreases according to the years. Talamonti et al. [15] demonstrated that at the end of the XX century mortality of MMC patients was about 2%. In our observation mortality was quite low and was 2.5%.

The results of our study are in accordance to the other studies about the localization of MMC where the most often is lumbar localization [19–22]; although in our study Th-L localization was quite frequent. Bulbul et al. [18] found Th-L level only in 7.1% patients. This difference can result from the time of damaging factors action in pregnancy. As is well known, the multiple initial closure is proposed for human neurulation sequence and the onset is estimated not later than the embryonic age day 24 [23]. The detection of the risks factors in this short time can be impossible.

Our results about follow-up in outpatient clinics differ compared to others. In other studies quite a big number of MMC patients did not see a nephrologist up to the age of 4.2 years and stayed under the care of pediatricians and urologists [24]. We have been carrying out the diagnostic program for many years in cooperation with other specialists, realizing that MMC patients are in the risks group of chronic renal diseases. Our attitude comes from our unpleasant experience with not catheterized patients which finally required renal replacement therapy. We started very early education to refer MMC patients to a nephrologist for renal function estimation.

Commonly, we are convinced that patients with S lesion localization have normal bladder function. Although, based on our analysis, we can say that firstly only one patient had correct bladder function and secondly 46% of well-activity patients need catheterization; it is evidence that there are plenty of patients with low lesion and incorrect bladder function.

Proportions in urodynamically confirmed lower urinary tract abnormalities are compared to others where the NDO was most common [25, 26]. The differences in other urodynamic diagnoses can come from the differences between groups and time of estimation.

Poor osmolality and lack of differences between 4 age groups can point out to renal function damage and in combination with higher eGFR in MMC patients can be recognized as a very early marker of renal function deterioration. In our study like in others [20] we did not find chronic renal diseases in any cases at first estimation.

Many studies have been conducted to evaluate factors reducing the prevalence of meningomyelocele but studies which organized to prevent or reduce renal function deterioration are still limited. In our study, we would like to make the assessment very early and have good cooperation of many specialists in our hospital. We recommend early institution of a bladder management program and a long-term follow-up of MMC patients. It is very important to find a proper way for early identification of children with high risk of renal failure. We should start from pregnant women, whose children are antenatally diagnosed with MMC and refer them to multidisciplinary, tertiary care hospitals with multi-specialist support. The next very important point of follow-up is annual urodynamically estimated bladder function and nephrologist consultation to detect renal function deterioration. In our opinion early CIC recommendation improves renal tract function and preserves progression to renal insufficiency.

Our study has some limitations. Firstly, we do not have the data concerning folic acid supplementation used by the MMC children's mothers. We have organized the questionnaire based on the study to complement the data of MMC children from our region. Secondly, we realized that all the described patients cannot be with MMC from our region and the data are not completed in all cases, but most of the MMC patients visited our tertiary center at least once. Additionally, we do not assess the influence of rehabilitation procedure on the physical activity of MMC children and neurogenic bladder function.

Conclusions

1. Data of MMC children from Poland are similar to the other countries.
2. In our opinion, early diagnostic and treatment procedure especially with early catheterization of MMC children prevent renal failure development.
3. Assessment of very early markers in renal function deterioration in neurogenic bladder patients from widespread multicenters research is indicated.

Authors' contributions/Wkład autorów

AK-K – study design, data collection, statistical analysis, data interpretation, acceptance of final manuscript version, literature search, funds collection. BK-B – data collection interpretation, acceptance of final manuscript version, literature search. BO-Z – data collection interpretation, literature search. TL-K – data interpretation, acceptance of final manuscript version, literature search.

Conflict of interest/Konflikt interesu

None declared.

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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