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Is there a correlation between structural changes of the bladder wall and its dysfunction? A Prospective Study

Czy istnieje korelacja między ultrastrukturą ściany pęcherza neurogennego a wynikami badań urodynamicznych?

Paweł Kroll[1, A, B, E, F], **Magdalena Sobieska**[2, C], **Anna Jażdżewska**[1, A, B, E, F], **Jakub Żurawski**[3, D], **Ewa Gajewska**[4, C]

[1] Pediatric Surgery and Urology Clinic, Neurourology Unit, Poznań University of Medical Sciences, Poznań, Poland
[2] Department of Rehabilitation and Physiotherapy, Poznań University of Medical Sciences, Poznań, Poland
[3] Department of Immunobiochemistry Chair of Biology and Environmental Protection, Poznań University of Medical Sciences, Poznań, Poland
[4] Department of Developmental Neurology, Poznań University of Medical Sciences, Poznań, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

The aim of the study was to evaluate the microscopic structure of the bladder wall in children with a neurogenic bladder to find a correlation between changes in the microscopic structure of the bladder wall and functional disorders. The study group consisted of 42 children who underwent bladder augmentation. Full-thickness fragments of the bladder wall were collected during operation, photographed for evaluation with a morphometric analysis. The proportion of muscle and connective tissue was determined. Results were correlated with the results of urodynamic tests. The analysis showed a progressive increase in connective/muscle tissue ratio with a decrease in the number of nerve trunks with a correlation between the connective/muscle tissue ratio and the deterioration of lower urinary tract in urodynamic investigations. Dysfunctions of the bladder are associated with histological abnormalities of the bladder wall, particularly increases in the amount of connective tissue and reduction of the number of nerve trunks. The increase in the percentage of the connective tissue correlates positively with deterioration of bladder function, reduced compliance of the bladder wall, and changes in the structure of the bladder wall and deterioration of the upper urinary tract.

Keywords: **neurogenic bladder • bladder wall • histology • complications • child**

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Author's address: Paweł Kroll, Dr. med., Pediatric Surgery and Urology Clinic, Neurourology Unit,Poznań University of Medical Sciences, 61-512, Poznań, ul. Pamiątkowa 2/42, Poland, e-mail: pawelkroll.poczta@gmail.com

INTRODUCTION

The role of the lower urinary tract is to store and periodically release urine. These are complex processes controlled by the central and the peripheral nervous system. A neurogenic bladder (NB) is a bladder that fails to perform its function and does not cooperate properly with the sphincters as a result of a known pathology within the nervous system. The most common cause of NB in children are congenital malformations of the spinal cord in the form of meningomyelocele (MMC). Less commonly, NB is caused by tethered cord syndrome, lipomas, or sacral agenesis. The post-traumatic injuries, which serve as the most frequent cause of NB in adults, rarely occur in children. Severe complications of bladder dysfunction may also develop in children as a result of other congenital defects, such as bladder exstrophy or posterior urethral valves (PUV) [9, 19].

The consequences of untreated or unsuccessfully treated NB during childhood are very serious, especially when they are diagnosed with a high intravesical pressure. No control over the detrusor contractions and the lack of their coordination with the relaxation of the sphincters generates high pressure in both the storage and voiding phases. An increase in pressure above the 40 cm H_2O detrusor Leak Point Pressure (LPP) is of prognostic value for the development of urinary tract complications [9, 19].

Since 1972 clean intermittent catheterization (CIC) has been the standard of care for the management of patients with NB. Additional treatment with anticholinergics allows pressure reduction and improvement in patient continence [9, 19]. However, complications develop in some patients despite pharmacotherapy and CIC. In those cases, surgical treatment may be considered necessary. Uretero-cutaneostomy or vesicostomy provide effective protection for the upper urinary tract, but may adversely affect patients' quality of life and cause urinary incontinence. Bladder augmentation (BA) is effective in reducing pressure in the urinary tract without causing urinary incontinence [5, 14].

It is unclear why the development of complications is only avoided in some patients with NB treated conservatively. We hypothesized that the answer to this question may lie in the morphological structure of the NB wall. The aim of our study was to assess the relationship between microscopic bladder wall morphology and urodynamic functional disorders in children with NB.

OBJECTIVES

The objectives of the present study include a prospective evaluation of the microscopic structure of the bladder wall in children with severe bladder dysfunction and a correlation between changes in the microscopic bladder wall and urodynamic functional disorders.

MATERIAL AND METHODS

The study was approved by the Bioethics Committee of the University of Medical Sciences in Poznań (Resolution No. 198/05).

A prospective analysis was conducted in a group of children undergoing surgical procedures for complications of NB that developed despite conservative treatment. The study group consisted of 42 children aged 2 to 18 years (mean age 8.5 years) who underwent BA in the Department of Pediatric Surgery and Urology at the University of Medical Sciences in Poznań between 2001 and 2004.

Causes of bladder dysfunction included MMC (n = 34): lumbrosacral defect (n = 28), sacral defect (n = 4), and thoracic region defect (n = 3). Other causes of NB dysfunction included occult spinal dysraphism in 3 children and cerebral palsy in one case. Three boys showed symptoms of bladder dysfunction after PUV resection, and in one case the cause was bladder exstrophy.

Video-urodynamic tests (VUD) were performed routinely according to the recommendations of the International Children Continence Society – ICCS.

Full-thickness fragments of the bladder wall of the 1x1cm dimensions were collected during the BA procedure. These were subsequently preserved in a 4% formalin solution. The collected tissue was stained using the Sirius method and neuron-specific enolase (NSE). The preparations were evaluated at 20x magnification, photographed, and 30 to 50 photos were taken for each preparation. Photos of the preparations were subject to morphometric analysis and the proportion of the muscle and connective tissue was determined using the ImageJ software (Image J developers). Sirius method is one of the best-understood techniques of collagen histochemistry. Immunohistochemical staining with neuron-specific enolase (NSE) was performed using mouse anti-human antibodies, clone BBS/NC/VI-H14 (Dako, Agilent Technologies), marking nervous cells. It identified bundles of nerve fibers present in the bladder muscles. The number of nerve trunks was evaluated in the subsequently viewed 30 FOVs for each preparation.

The control group consisted of sample tissues collected from 12 bladders of children, aged 2 to 12 years, who died for reasons not related to the urinary system (e.g., heart defects, accident victims). Results obtained from

a microscopic examination of the bladder wall from each child in the study group were correlated with the results of urodynamic tests performed prior to the surgery.

STATISTICAL METHODOLOGY

The results related to the number of children with normal or abnormal bladder function in the study groups were compared using a test for the difference between structure indicators (frequency expressed as a percentage).

The results of the connective tissue/muscle tissue ratio were compared between the study groups (1 to 5) using the Kruskal-Wallis test, which initially verifies whether there are at least two groups that differ significantly. Subsequently, the Dunn test was used to compare the differences between all groups. Correlations within the study groups, between the connective tissue/muscle tissue ratio and the number of nerve trunks, were analyzed using Pearson's correlation coefficient.

The results were considered statistically significant at the significance level of $p < 0.05$.

The statistical analysis was performed using the Statistica PL v. 7 software. 1 (StatSoft Inc.).

RESULTS

Urination Method

CIC was applied in 30 children. Ten children had a permanent urinary diversion, 2 through Blocksom vesicostomy and 8 through indwelling catheters (6 Foley, 2 suprapubic). In two children who were voiding spontaneously, no additional methods to empty the bladder were used before BA.

Additional Morbidity – Defecation Control

Out of 42 children enrolled in the study, 16 defecated independently and regularly and 26 manifested a significant degree of constipation, including three patients with Mitroffanof-Malone appendicocutaneostomy for antegrade colonic enemas.

Additional Test Results

An abdominal ultrasound showed dilatation of the upper urinary tract in 39 children, of which hydronephrosis (HDN) was found in 21 children and megaureters (MU) in 18 children. VUD examinations were performed in all patients qualified for BA. In 36 children, there was no sensation of the urethra. Sensation of the urethra was preserved in 6 children, 3 of whom had decreased sensation. There was no bladder filling sensation in 35 patients, but it was normal in 5 patients and only decreased in 2 patients. Stable detrusor was found in 2 children, while overactive detrusor contractions were observed in 40 patients. Compliance was high (normal) in 5 children, decreased in 13 children, and low (< 10 mL/cm H_2O) in 24 children. Electromyographic evaluation of the sphincter function was performed in 13 children, and 11 of them were diagnosed with the lack of detrusor-sphincter coordination. Increased detrusor LPP was found in 41 patients, of which 19 children had LPP between 40 and 70 cm H_2O, 13 children had LPP between 70 and 100 cm H_2O, and 9 children had LPP greater than 100 cm H_2O. VUD revealed vesicoureteral reflux (VUR) in 24 patients, in whom bilateral VUR was found in 8.

VUD examination also provided for the assessment of shape and outline of the bladder wall. A normal, regular bladder wall was found in 4 children, irregular outline of the wall was found in 16 patients, trabeculation of the bladder wall was observed in 6 children, the presence of multiple diverticula was observed in 14 patients, and in 1 case a large, single diverticulum was found.

Microscopic Evaluation of the Bladder Wall Tissue Samples

The connective tissue to muscle tissue ratio was determined for both the study and control groups (Table 1).

The analysis showed that the connective tissue/muscle tissue ratio was five-times higher in the study group compared to the control group.

Number of Nerve Trunks

The number of nerve trunks was determined in patient bladder wall fragments from the study group and the control group. Given the results, the patients were classified into six groups according to the number of nerve trunks. We compared the number of nerve trunks in the examined bladder wall tissue samples with the connective tissue/muscle tissue ratio. An extremely large number of nerve trunks (>40) was found in only 2 patients from the study group. Table 2 shows the number of nerve trunks in the six groups of patients and the correlation between the number of nerve trunks and the connective tissue/muscle tissue ratio.

The analysis showed that the most favorable connective tissue/muscle tissue ratio (1.05) was found in patients with more than 40 nerve trunks in the bladder tissue samples. Statistically significant differences were shown between groups 1 and 4, 5 and 6 ($p < 0.003$), and 2 and 5 ($p < 0.002$). Figure 1 and 2 show samples from the bladder wall (Sirius staining) from the study group and control group, respectively.

The analysis of individual groups of patients showed a progressive decrease in the connective tissue/muscle tissue ratio combined with an increase in the number of nerve trunks. A significant breakthrough in the correlation was observed starting with group 4 and higher.

A comparison of morphological changes in the bladder walls and segments of the spinal cord injury was performed in the study group. No correlation was found

Table 1. The connective tissue to muscle tissue ratio for both the study and control groups

Connective tissue/muscle tissue ratio	Value range	Mean value	Standard deviation
Study group n = 42	1.0–22.48	1.53	0.317
Control group n = 12	0.14–0.64	0.28	0.142

Table 2. The number of nerve trunks in the study group and correlation between the number of nerve trunks and the connective tissue/muscle tissue ratio

Group	1	2	3	4	5	6
No of nerve trunks	≤10	10–15	16–20	21–30	31–40	>40
No of patients	7	15	4	8	6	2
Connective tissue/ muscle tissue ratio (mean value)	2.02	1.66	1.46	1.33	1.16	1.05
Standard deviation	0.262	0.105	0.033	0.034	0.060	0.042

between the degree of spinal cord defects and the connective tissue/muscle tissue ratio. We also correlated the connective tissue/muscle tissue ratio in the bladder wall with its function as determined by VUD examination. The study group was divided into three groups (A, B, C) based on connective tissue/muscle tissue ratio. Group A consisted of 7 children and was predominantly characterized by detrusor stability, high bladder compliance, and a regular shape of the bladder in the VUD examination. The features that were prevalent in group B included detrusor overactivity, reduced compliance, and the presence of diverticula and trabeculation. Group C showed detrusor overactivity, low compliance, and irregularity of the bladder wall with diverticula. Table 3 shows a comparison of the connective tissue/muscle tissue ratio and bladder function upon VUD examination in the three groups.

Statistical Analysis of the Structure and Functions of the Bladder

A statistical analysis was performed on the correlation between connective tissue/muscle tissue ratio in the bladder wall and its functions. Correlation of the detrusor contractility and bladder wall compliance was investigated in the three groups described above (A–C).

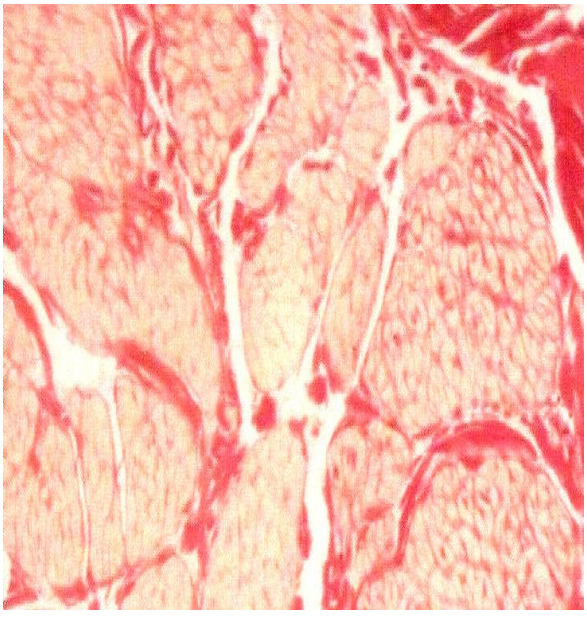

Fig. 1. Study group, neurogenic bladder

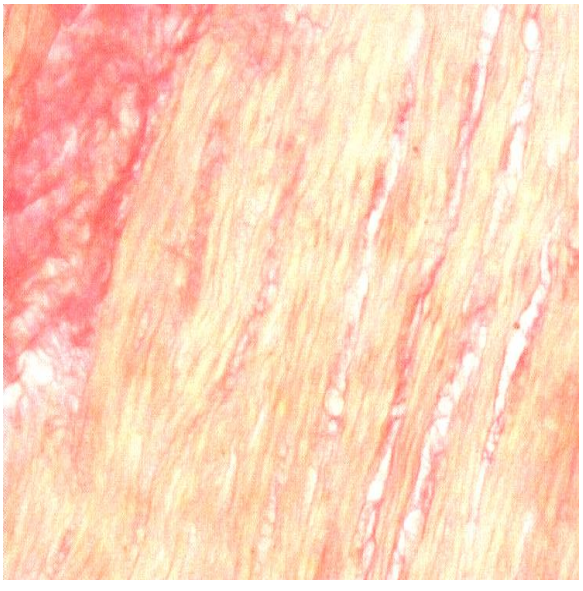

Fig. 2. Control group, normal bladder; Sirius staining–red: connective tissue, yellow: muscle tissue

Table 3. Comparison of the connective tissue/muscle tissue ratio with the bladder function in the VUD examination

Connective tissue/muscle tissue ratio	No of children	Detrusor function	No of children	Bladder wall compliance	No of children	Bladder wall	No of children
A: 1.02–1.2	7	S	4	N	4	R	5
		O	3	D	3	T	2
				L	0		
B: 1.21–1.5	12	S	1	N	1	T	7
		O	11	D	7	DI	5
				L	4		
C: 1.51–2 and above	23	S	0	N	0	T	12
		O	23	D	6	DI	11
				L	17		

Legend: S – stable, O – overactive, N – normal, D – decreased, L – low, R – regular, DI – diverticula, T – trabeculation

In group A, 3 children showed abnormal function of the detrusor. In the other two groups, all children showed features of abnormal bladder function. The compliance of the bladder wall was reduced in 5 of 7 children from group A, 11 from group B, and all from group C. The analysis showed significant differences in the function of the detrusor between groups A, B, and C ($p < 0.005$). Bladder wall compliance was significantly abnormal in groups A and C ($p < 0.001$).

Pathologic changes of the bladder wall structure in the form of diverticula, trabeculation, and irregular outline of the wall were found in 2 children from group A, and all of the children from groups B and C. Abnormalities in the bladder wall structure were considered significant between groups A, B, and C ($p < 0.005$).

Statistical Analysis of the Morphology of the Bladder Wall and Changes in the Upper Urinary Tract

A statistical analysis was also performed on the correlation between connective tissue/muscle tissue ratio in the bladder wall and anatomical changes in the upper urinary tract. The incidence of VUR, MU, and HDN was evaluated in the three selected groups of patients. The results were compared with the number of patients in each group and the reported abnormalities were expressed as percentages taking into account the significance level. In group A, the smallest number of children showed the presence of VUR. MU was found in 1 child from group A, 6 from group B, and 13 from group C. HDN was found in 3 children from group A, 3 from group B, and 6 from group C. The analysis showed a borderline significant difference in the number of children with MU between groups A and C ($p = 0.0584$). For the other parameters, VUR and HDN, differences were not statistically significant due to the small size of the groups.

DISCUSSION

NB is a dysfunction of the lower urinary tract caused by an acquired disease or a congenital defect of the nervous system. MMC is the most common cause of NB in children. The introduction of CIC and the use of anticholinergics have significantly improved treatment results and quality of life in patients with NB. However, some patients develop complications despite conservative treatment. The aim of BA is to increase the volume of the bladder and decrease the intravesical pressure. BA is proposed for patients with NB and complications that develop despite conservative treatment. During BA operation the bladder wall is widely incised or partly excised [5, 9, 14, 19]. We have proposed our own practical classification of complications characteristic of children with bladder and sphincter dysfunctions [9]. In the present study, we performed a macroscopic and microscopic evaluation of the bladder wall morphology in children eligible for the BA procedure to determine whether a correlation exists between the histological structure and the abnormal bladder function. The analysis included 42 children, with slightly more females than males. Previous studies on this issue involved a similar number of patients, with only a few authors analyzing a larger group of patients [2, 3, 4, 8, 10, 12, 15, 18].

In our material, as well as in a study by Lee [11], the prevailing group included children with MMC in the lumbosacral region, with other individual cases of bladder dysfunction caused by cerebral palsy, PUV, or bladder exstrophy. Similar groups of patients were analyzed in other studies [2, 3, 4, 8, 10, 11, 12, 15, 18]. In the VUD examination, parameters considered to be the most important included the presence of bladder sensation, sensation of the urethra, detrusor overactivity, LPP, and compliance. We also focused on the shape and outline of the bladder wall and the presence of VUR.

Absence of bladder and or urethra sensation was found in the majority of our patients. The compliance of the bladder walls was reduced in more than 90% of the children in the study group and detrusor overactivity was found in the vast majority of these children. These phenomena tended to co-occur with elevated LPP and the generation of high intravesical pressures. High pressure leads to a disturbance of the blood supply in the bladder wall and the development of secondary lesions, including thickening, trabeculation, and formation of diverticula [4, 5, 9, 11, 14, 16, 17, 19]. The results of US examinations play an important role in the follow-up of patients with NB [9, 19].

HDN, MU, thickening of the bladder wall, and diverticula were found in the majority of patients participating in this study. Other authors reported similar changes in the urinary tract in patients with bladder dysfunctions. Seki [16] found the presence of VUR in 1/3 and HDN in 1/5 of children with NB. Simforoosh [17] observed VUR in all patients with NB qualified for BA and the presence of HDN in the majority of them. Ghanem [4] analyzed patients with valve bladders and showed results similar to ours, where almost half of the patients presented VUR and more than 3/4 had HDN.

Identifying all urodynamic parameters in newborns is difficult due to their lack of cooperation with the investigator, so the most important element is the LPP evaluation due to its prognostic value [5, 11, 15, 19]. In all children participating in our study, LPP was >40 cm H_2O and complications developed despite conservative treatment.

There are few articles in the literature correlating microscopic structure of the bladder wall with NB function. The methodology of the study by Özkan [15] was similar to ours, with microscopic examinations performed in a group of 39 children with NB complications. The author concluded that the severity of detrusor fibrosis was a significant risk factor for upper urinary tract deterioration. Landau et al. [10] collected fragments of the bladder wall from patients with abnormal results of urodynamic examinations and all had upper tract changes and/or were incontinent despite conservative treatment with CIC and pharmacotherapy. They showed the dominance of the connective tissue over the muscle tissue, with connective tissue levels over three times greater. Additionally, they investigated the correlation between the collagen type I and III, reporting the dominance of type III. They concluded that the poor storage function of a poorly compliant bladder is secondary to an alteration in the connective tissue content of the bladder wall. Tse [18] published the results of examinations of the ultrastructure of the bladder wall conducted on 27 children with NB. An examination using an electron microscope revealed significant changes in the structure of the bladder wall, including myohypertrophy and abnormal junctions in all patients. A correlation between changes in the histological structure and functional disorders shown in urodynamic tests was reported. Haferkamp [7] also performed an electron microscopic examination of the bladder wall of 46 patients with a NB and confirmed that NB dysfunction is associated with intrinsic neuromuscular defects in the detrusor, whereas Mills [12] demonstrated that the basis of the abnormal function of the detrusor lies in its innervation and the cellular structure.

Other studies showed degeneration of muscle fibers in patients with NB, causing secondary ischemia and abnormal distribution of metabolites within the detrusor muscle cells [2, 8]. El Badawi [3] pointed out that the extent of lesions in NB muscle may depend on the degree of the nervous system damage. Gosling [6], using an animal model, demonstrated the correlation between the duration of the presence of an obstruction and a decrease in the sensitivity of muscle cells to a stimulus, accompanied by their damage. The author observed damage to the mitochondria in the blood vessel cells of the obstructed bladder wall. It was thus shown that the wall of NB or of a dysfunctional bladder demonstrates several abnormalities, including abnormal proportions in the number of receptors, a reduced number of nerve fibers, abnormal connective tissue/muscle tissue ratio, and pathology in the structure of muscle cells. All of these elements may also underlie the dysfunctions of a NB [1, 2, 3, 6, 7, 8, 10, 13, 15, 18].

The most obvious limitation of our study is the small sample size necessitated by the fact that BA is performed only in a small percentage of children with complications of NB. The heterogeneity of the group also presents a limitation. While the majority of children had myelomeningocele, there were several other causes of bladder dysfunction represented in the group. However, changes in histopathology were similar for all of the children in the study group.

The results presented here demonstrate a correlation between changes in the microscopic structure of the bladder wall and the degree of deterioration in the upper urinary tract. This deterioration is also correlated with an increase in the amount of connective tissue present in the bladder wall. In addition, we observed fewer muscle fibers and nerve trunks in abnormally functioning bladders compared to the control group. It is likely that the growth of connective tissue caused a separation of nerve trunks, which may decrease the conduction of nerve impulses. As these changes are irreversible, surgical procedures should be considered for such children. We observed a significantly higher connect tissue/muscle tissue ratio in children with NB compared to children with healthy bladders. Moreover, we found a statistically significant correlation between the connective/muscle tissue ratio and increased severity of changes in bladder function, associated with abnormal parameters of bladder function in VUD examinations.

CONCLUSIONS

Functional and structural dysfunctions of the bladder are associated with histological abnormalities of the bladder wall, particularly related to increased amounts of connective tissue and a reduced number of nerve trunks. The increase in the percentage of connective tissue relative to muscle tissue correlates positively with the deterioration of the bladder function expressed by detrusor overactivity, reduced compliance of the bladder wall, changes in the structure of the bladder wall (trabeculation and diverticula), and deterioration of the upper urinary tract.

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