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Factors Affecting Renal Scar Development in Children with Spina Bifida

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Key Words
Kidney · Risk factors · Spina bifida

Abstract
Background/Aims: Prevention of renal scarring is the main therapeutic goal in children with spina bifida. We aimed to determine factors affecting renal scar development in these patients. ***Materials and Methods:*** Records of 312 children admitted between 1994 and 2005 with spina bifida were reviewed. Age on admission, gender, presence of previous febrile urinary tract infections (UTIs), vesicoureteral reflux (VUR), and initial urodynamic findings were noted. Patients were grouped regarding presence/absence of renal scars on DMSA scans. χ^2 and Student's t tests were used for statistical evaluation. ***Results:*** Seventy-two patients had renal scars on admission. Mean age was 4.62 ± 4.59 years for patients without renal scars and 6.35 ± 4.9 years for patients with scars. Male/female ratio was 1:1 in the scarless group and 1:2 in the group with scars. Previous febrile UTI was present in 11 of 240 scarless patients in contrast to 7 out of 72 patients in the scar group ($p > 0.05$). VUR was present in only 16.3% of cases without scars, whereas 36.1% of patients in the scar group had VUR. Detrusor overactivity and detrusor sphincter dyssynergia were observed in 67.1% of scarred patients, whereas this figure was 42.4% in the scarless group. The comparison of age on admission, gender, detrusor overactivity, and detrusor sphincter dyssynergia revealed significant differences between patients with and without renal scars. ***Conclusions:*** Late referral, female gender, overactive detrusor, and detrusor sphincter dyssynergia have detrimental effects on renal parenchymal function in spina bifida patients. Patient selection for aggressive treatment using these features may prevent renal parenchymal deterioration.

Introduction

Prevention of renal scarring is the main therapeutic goal in children with spina bifida. Chronic renal failure and its complications are among the most frequent cause of morbidity and mortality in these patients [1]. Aggressive surgical measures are mandatory such as augmentation cystoplasties when medical treatment modalities fail to prevent scar formation. Thus, the tendency has always been towards early detection of cases who may carry the risk of renal scarring.

Several studies have been done regarding the risk factors for renal deterioration in myelodysplastic patients [2–6]. However, there are still controversies and debate about the exact definition of these factors. The aim of this study was to determine potential conditions that might have predictive value on future renal functions in children with spina bifida.

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Table 1. Analysis of renal scar on admission versus various factors

Variables	Renal scar on initial admission		p value
	absent	present	
Age, years	4.62±4.59	6.35±4.9	0.007*
Sex			
Males	121	24	
Females	119	48	0.02*
Previous febrile UTI			
Absent	229	65	0.176
Present	11	7	
VUR[1]			
Absent	90	32	0.076
Present	39	26	
VUR grade			
Low	22	6	
High	17	20	0.016*

* Denotes statistical significance. UTI = Urinary tract infection; VUR = vesicoureteral reflux.

[1] Patients in whom voiding cystourethrographies were not performed were excluded.

Table 2. Analysis of renal scar on admission versus urodynamic parameters

Variables	Renal scar on initial admission		p value
	absent	present	
Bladder capacity, % of expected capacity	69.9±43.6%	69.6±47.5%	0.976
Bladder compliance			
Low	184	58	0.508
Normal	56	14	
DLPP, cm H_2O	49.4±27.7	54.4±27.8	0.253
DSD			
Absent	138	24	
Present	102	48	0.001*
PVR			
Absent	101	22	0.121
Present	139	50	
Detrusor contractility			
Normal	50	5	
Areflex	18	6	
Overactive	172	61	0.034*
Sphincter contractility			
Normal	41	3	
Areflex	40	11	
Overactive	159	58	0.03*

* Denotes statistical significance. DLPP = Detrusor leak point pressure; DSD = detrusor sphincter dyssynergia; PVR = postvoiding residual urine.

Materials and Methods

Medical records of children who admitted to a single institution between 1994 and 2005 with the diagnosis of spina bifida were reviewed retrospectively. Age on admission, gender, history of previous febrile urinary tract infections (UTIs), vesicoureteral reflux (VUR) and initial urodynamic findings were noted. Patients were grouped according to presence or absence of renal scars on initial admission.

Patients were questioned about demographic data, symptoms, previous history of the disease including former febrile UTIs or genitourinary anomalies. They were also evaluated routinely with urine analyses, urine cultures, renal and bladder ultrasonographies (USGs), voiding cystourethrograms (VCUGs) and dimercaptosuccinic acid (DMSA) renal scans if indicated, and urodynamic investigations. Febrile urinary tract infections were defined as having fever over 38°C with confirmed bacterial growth of over 100,000 colony-forming units (cfu) per milliliter in urine cultures and without any other cause of fever. Renal and bladder USGs and VCUGs were obtained for detection of hydronephrosis, bladder trabeculations, and VUR. VUR was defined according to guidelines of International Classification [7]. Renal scars were investigated with DMSA scans. Findings of contour irregularities, and defects were accepted as indicative for renal scarring.

A multichannel cystometry was performed with PC Polygraph Uro (Synetics Medical AB, Stockholm, Sweden). Actual bladder capacity (% of expected capacity) and compliance (ml/cm H_2O), detrusor leak point pressure (DLPP) (cm H_2O), contractility of detrusor and pelvic floor and postvoiding residual urine (ml) were studied in these patients cystometrically. Expected bladder capacity (EBC) was determined according to the formula EBC (ml) = (age + 2) × 30. Compliance below 20 ml/cm H_2O was considered as low, DLPP over 40 cm H_2O as high and postvoiding residual volume over 10% of actual bladder capacity was accepted as high. Urodynamic studies were performed using 6-Fr double lumen cystometry catheters, rectal catheters and electromyographic electrodes in sitting position at a filling rate of 10% of expected bladder capacity in milliliter per minute with 37°C warmed saline solution. Abdominal pressures were monitored with the rectal catheters and pelvic floor activity with the AgCl perianal electrodes during the procedure. Findings were defined according to the guidelines of the Standardization Committee of the International Children's Continence Society [8].

For statistical analysis, nominal values were evaluated with the chi-square test and numeric values with Student's t test. $p < 0.05$ was considered statistically significant.

Results

A total of 312 medical records were reviewed retrospectively. Seventy-two patients had renal scars on admission according to DMSA scans. Mean age was 6.35 ± 4.9 years for patients with renal scars and 4.62 ± 4.59 years for patients without scars ($p = 0.007$) (table 1). There were 48 females and 24 males in the scar group and 119 females and 121 males in the scarless group. Male/female

ratio was 1:2 in the group with scars and 1:1 in patients without scar. The difference between two groups was statistically significant ($p = 0.02$).

A history of previous febrile UTI was present in 11 of 240 scarless patients in contrast to 7 out of 72 patients in the scar group ($p > 0.05$). VUR was present in only 16.3% of cases without scars, whereas 36.1% of patients in the scar group had VUR. The comparison between these two groups for the presence of VUR was not statistically significant ($p = 0.076$). However, in the scarless group, 22 out of 39 children (56.4%) had reflux equal and lower than grade 3, whereas only 6 patients (23.1%) had VUR below grade 3 in the scar group. High-grade VUR was found to be statistically more often in the scar group ($p = 0.016$).

Detrusor overactivity and detrusor sphincter dyssynergia were observed in 67.1% of scarred patients, whereas this figure was 42.4% in the scarless group. Detailed analysis with urodynamic findings are summarized in table 2.

Other cross-comparisons of risk factors like genitourinary anomalies between each other were statistically insignificant.

Discussion

Chronic renal failure and its consequences are among the most important cause of morbidity and mortality in spina bifida patients. Thus, main therapeutic aim in the management of these patients is early detection of neurourological dysfunction and prevention of renal scarring. About 10–30% of children are born with the evidence of upper urinary tract pathology and this figure increases to approximately 50 % by the age of five [9]. Recent reports suggest that early detection of the pathology and follow-up with proper treatment result in excellent renal preservation and a safe method of management [10–12]. Newborns during this follow-up have been observed to be at risk for neurological deterioration especially in the first 6 years of life [12]. According to Seki et al. [6], age is not a determinant factor for renal deterioration. This study revealed a significant difference in age group in terms of renal scarring emphasizing the necessity of early proper treatment and referral which is still a problem in some areas.

The role of gender as a risk factor for renal scarring is controversial in spina bifida. There is very little information about this subject in the literature. Kurzrock and Polse [2] postulated that female gender is a risk factor for renal deterioration in myelodysplastic children as girls experience more primary VUR and urinary tract infection than boys and there is no significant difference between the urodynamic findings of boys and girls. Teichman et al. [13] have also emphasized three significant risk factors for deterioration including female sex, infection and reflux. Wennerström et al. [14] found in a population without spina bifida that girls develop more renal scars due to recurrent febrile urinary tract infections; on the other hand, boys mostly develop scars due to VUR. Nevertheless, Seki et al. [6] saw that female sex did not make a difference in renal deterioration. In this study, female patients were found to be more likely to develop renal scarring in spina bifida. Cross-comparison of female sex and other factors such as febrile UTI, VUR, and urodynamic parameters were statistically insignificant pointing out female gender as a possible independent risk factor.

Renal damage is mostly associated with history of febrile UTI and VUR other than age in children with spina bifida [4]. Decreased bladder compliance, detrusor overactivity, bladder trabeculation and VUR have been found to be correlated with the cause of febrile UTI in myelodysplastic children [15]. Prevention of UTI besides VUR is also important as acute pyelonephritis may contribute to the progressive scar formation [1]. UTI has been accepted as a definite risk factor for renal scarring [2]. However, in the patient population of this study, previous febrile UTI was found to be statistically unrelated to further scar formation.

VUR is commonly a result of increased intravesical pressure in myelodysplasia [16]. This condition is well defined to have detrimental effects on renal function in this patient group [2, 6]. Prediction of patients who are resistant to conservative management of VUR with clean intermittent catheterization, anticholinergic drugs and surgery may also prevent prolonged risk of renal damage [17, 18]. On the other hand, the incidence of VUR was not found to be a statistically significant risk factor for scar formation in this study. However, when high grade reflux was considered, this parameter was found to be significantly higher in the scar group. The majority of these patients also had low compliant, high pressure bladders with overactive detrusor and pelvic floor, signifying the worst status in terms of bladder function. Female gender has been accused of being a risk factor both in myelodysplasia and normal population as it potentiates VUR [2, 19]. The same findings were not observed in this study in myelodysplastic children with neither low nor high grade VUR.

Urodynamic studies have been widely accepted to have prognostic value in patients with spina bifida. There is almost consensus about the predictive role of detrusor sphincter dyssynergia for urologic complications [2, 6, 20, 21]. The same findings were also observed in this study. However, there is still controversy about other urodynamic parameters. Maximum urethral closing pressure has been shown to predict renal outcome in myelodysplastic children [6, 22]. This parameter is mostly replaced with the measurement of DLPP and pelvic floor electromyography in contemporary practice. DLPP and bladder compliance are the other parameters which have been shown to act as a predictive factor in myelodysplasia [2, 5, 22]. Findings in this study revealed that these factors were irrelevant to scar formation. Other parameters like bladder capacity and residual urine after voiding were also found to be insignificant. Only overactive detrusor function was found to be increased in the scar group ($p < 0.05$).

In conclusion, late referral clearly increases the risk of renal scarring in myelodysplastic children, emphasizing the need for early and prompt onset of treatment. Female gender may have an independent detrimental role which is difficult to explain with coexisting findings. Higher grades of VUR increase the risk for kidney damage as expected. Overactive detrusor function with or without sphincter dyssynergia should be a warning sign for future renal scarring if not treated timely and properly. Patient selection for aggressive treatment using these features is critical in order to prevent renal parenchymal deterioration in myelodysplastic children.

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