Factors related to renal deterioration in children and young adults with spina bifida: A longitudinal study using dimercaptosuccinic acid scans

Yuichiro Yamazaki (✉ yuichiroy@gmail.com)
Kanagawa Children's Medical Center

AYAKO GOHBARA
Kanagawa Rehabilitation Hospital

Rumiko Eura
Kanagawa children's medical center

Morihiro Nishi
Kanagawa children's medical center

Tomomi Nishikawa
Kanagawa children's medical center

Koji Yamamoto
Kanagawa children's medical center

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标题：

因素与脊髓裂相关的儿童和年轻人肾功能衰退：纵向研究使用二硫代丁二酸钠扫描

Kota Shimokihara¹, Ayako Gohbara¹, Rumiko Eura¹, Morihiro Nishi¹, Tomomi Nishikawa², Koji Yamamoto² and Yuichiro Yamazaki¹*

¹Department of Urology, Kanagawa Children’s Medical Center, Yokohama, Japan.
²Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan.

*Corresponding author:

纵向研究用于脊髓裂

关键词

脊髓裂, 肾损伤, 二硫代丁二酸钠, 膀胱, 儿科
ABSTRACT (max 250 words)

Study Design: Retrospective, cohort study

Objectives: First, to investigate the prevalence of new DMSA abnormalities by age in patients with spina bifida, and second, to evaluate the age differences in risk factors for new DMSA abnormalities.

Setting: Children’s hospital in Yokohama, Japan

Methods: All patients with spina bifida requiring clean intermittent catheterization who visited from 2009 to 2021 were enrolled. Inclusion criteria consisted of having at least two DMSA scans performed at age ≤12 years and ≥13 years. Patients with no sequential data from video urodynamic studies were excluded. Risk factors for new DMSA abnormalities were evaluated in two different growth stages (age ≤12 years, age ≥13 years).

Results Fifty-seven patients with a median follow-up of 18 years were included. At the end of the study, 22 patients (39%) had DMSA abnormalities. The number of patients having new DMSA abnormalities in childhood (age ≤12 years) and in young adulthood (age ≥13 years) was 10 (18%) and 12 (21%), respectively. After the LASSO logistic analysis, three variables (maximum detrusor pressure, vesicoureteral reflux, and bladder trabeculation) were identified as factors related to new DMSA abnormalities in children.
On the other hand, vesicoureteral reflux was the only related factor in young adults.

**Conclusions**: In children with spina bifida, there was no age tendency in the development of new DMSA abnormalities. Vesicoureteral reflux was related to new DMSA abnormalities in both **childhood and young adulthood**. However, video urodynamics parameters were related to new DMSA abnormalities only in childhood.
INTRODUCTION

The primary purpose of urological management in patients with spina bifida (SB) is preventing loss of renal function. Current guidelines for management of neurogenic bladder recognize the importance of kidney function surveillance, with all recommending periodic kidney imaging. (1-3) From the perspective of precise evaluation of renal cortical loss, the dimercaptosuccinic acid (DMSA) renal scan is still the gold standard for detecting renal cortical loss represented by renal scarring. (4) Previous reports evaluating renal scarring using DMSA scans in these populations have found scarring rates of 15-46%. (4-7) In our previous study, vesicoureteral reflux (VUR) history was one of the significant risk factors for an abnormal DMSA renal scan in children aged >10 years with SB. (8) To prevent renal deterioration in the children with SB, the age at which children are susceptible to new renal scarring should be investigated in a longitudinal study. Based on our previous study, we hypothesized that children aged ≤12 are more susceptible to renal cortical damage than teens and young adults. (8) To examine this hypothesis, the present study had two objectives: to investigate the prevalence of new DMSA abnormalities according to the age of patients with SB; and to evaluate the age differences in risk factors for development of new DMSA abnormalities in patients with SB.
METHODS

Study Design

This single-center, retrospective, cohort study was initiated after Institutional Review Board approval and waiver of informed consent requirements were obtained prior to data collection.

Patient selection

Since 2007, all patients with SB (including myelomeningocele, meningocele, spinal lipoma, and dermal sinus tracts) managed in our institution were entered into the institutional SB database. A retrospective chart review was performed of all patients included in the database from 2009 to 2021. The inclusion criteria were as follows: patients requiring clean intermittent catheterization (CIC) during the follow-up period; patients having at least two DMSA scans in childhood (age ≤12 years) and in young adulthood (age ≥13 years). The exclusion criteria were as follows: patients with no sequential data from biannual video urodynamic study (VUDS) examinations; and patients with concomitant abnormalities such as anorectal malformations. Indications to start CIC in our institution were inability to empty the bladder, unfavorable findings on VUDS (i.e., high DLPP >40 cm H₂O, presence of detrusor sphincter dyssynergia,
presence of VUR), or upper urinary tract dilatation on ultrasound.

**Outcomes**

The primary outcomes were the age differences in the prevalence of the new DMSA abnormalities in patients with SB. The secondary outcomes were the risk factors identified separately for new DMSA abnormalities occurring in childhood and those occurring in young adulthood. A DMSA abnormality was diagnosed if differential renal function was less than 40%, or focal cortical defects were seen on DMSA scans by a radiologist independently. To identify the risk factors for new DMSA abnormalities, six variables including sex, maximum cystometric capacity (MCC), maximum detrusor pressure (MDP), presence of VUR, presence of bladder trabeculation, and initiation of CIC after age 1 year were selected based on previous studies. All VUDSs were scored by five pediatric urologists (K.S., M.N., A.G., R.E., and Y.Y.).

**Follow-up of DMSA and VUDS examinations**

Since 2009, DMSA planar scintigraphy was routinely performed every 6 years in SB patients undergoing CIC in addition to the baseline DMSA scan in infancy or at the first referral. During follow-up, additional DMSA scans were scheduled in patients with suspected febrile urinary tract infections or new abnormal findings on VUDS. All DMSA renal scans were performed at least 4 months following a prior episode of febrile UTI.
VUDS was performed annually in patients aged 0-2 years, and biannually after age 2 years if no clinical symptoms occurred. For VUDS evaluation, the VUDS performed at the date nearest the DMSA scan was used. Standard fluid cystometry in conjunction with fluoroscopy was done with children in the supine position using a double-lumen urodynamics catheter and a rectal balloon catheter, filling at a rate of less than 10% of predicted bladder capacity per minute. Anticholinergic therapy was not discontinued before the VUDS. Radiographically, VUR and bladder trabeculation were evaluated at MCC. According to the International Children’s Continence Society report, MCC was defined as maximal tolerable cystometric capacity or capacity when leaking began.(9) MDP was defined as detrusor pressure at MCC or detrusor leak point pressure. VUR was graded by the international reflux grading system. Presence of VUR in this study was defined as grade 2 to 5. Bladder trabeculations were defined as irregularities in the contours of the bladder walls.

**Statistical Analysis**

To estimate the probabilities of occurrence of DMSA abnormalities by age, Kaplan-Meier survival curves using the log rank test was constructed for time to new DMSA abnormalities. On univariate analysis, patients’ characteristics and variables were assessed by Pearson’s chi-squared tests and Mann-Whitney U tests. On multivariate
analysis, LASSO regression analysis was performed to reduce the dimensionality of inputted variables and establish the prediction model of variables with non-zero coefficients. Five-time cross-validations were performed to identify the tuning parameter lambda. According to the best lambda value, a list of prognostic factors for DMSA abnormalities with coefficients was obtained from the prognostic factors estimated and patients’ DMSA data. LASSO regression model analysis was implemented using R software (<http://www.r-project.org>) and the “glmnet” package (<http://cran.r-project.org>).
Results

During the study period, 61 patients were enrolled, but 4 were excluded due to incomplete VUDS records. Therefore, 57 patients were included in study analyses. The median follow-up period was 18 years (IQR: 16-18 years). Table 1 presents the baseline characteristics of these 57 patients, 45 (78.9%) of whom had MMC. The median age at the DMSA scans in childhood and in young adulthood was 7 years (IQR: 7-10 years) and 18 years (IQR: 16-18 years), respectively.

DMSA abnormality-free survival was calculated by the Kaplan-Meier method with an average follow up of 17.1 years. Kaplan-Meier curves for patients free of DMSA abnormalities are presented in Figure 1. Of the 57 patients, 10 (18%) had DMSA abnormalities in childhood (age ≤12 years). At the end of the present study, 22 patients (39%) had DMSA abnormalities. Therefore, 12 patients (21%) developed a new DMSA abnormality in young adulthood (age ≥13 years).

Table 2 and 3 shows the results of univariate analysis of variables associated with new DMSA abnormalities in childhood and in young adulthood. On univariate analysis, MDP was significantly higher in the abnormal DMSA group than in the normal DMSA group in children. On the other hand, there was no significant difference in MDP between the groups with presence and absence of DMSA abnormalities in young adults.
On multivariate analysis, a LASSO logistic regression model was used to identify risk factors for DMSA abnormalities. After the LASSO logistic analysis, three variables (MDP, presence of VUR, and bladder trabeculation) were identified as factors related to new DMSA abnormalities in childhood. On the other hand, the presence of VUR was the only factor identified in young adulthood (Table 4).
DISCUSSION

Previous studies using DMSA scans to evaluate patients with SB have shown renal scarring rates of up to 46%.(4) Although renal bladder ultrasound (RBUS) has been widely used for kidney surveillance, ultrasound has a poor correlation with renal scars. Veenboer et al. evaluated 122 adults with SB with median age of 31.5 years (with 242 renal units) who underwent both renal scintigraphy and ultrasonography, and more scarring was seen on DMSA scintigraphy than on ultrasonography: 45.9% vs. 10.3% of renal units.(4) According to Ottorini et al., of 207 patients with neuropathic bladders who were practicing CIC, renal scarring was detected in 20% of children with a mean age of 11 years. Factors associated with renal scarring were febrile infections, age >20 years, the presence of bladder trabeculation, and VUR.(6) In our previous study, 64 patients with SB aged >10 years were evaluated, and 25%, with a mean age of 14.6 years, had abnormal DMSA scans. A positive VUR history and febrile urinary tract infections were associated with an abnormal DMSA scan.(8)

With respect to the prevalence of renal scarring by age, Lewis et al. showed that the parenchymal damage evaluated by DMSA scan in those aged >10 years (27.3%) in this population was twice that of those aged <5 (13.3%).(10)
However, most studies using DMSA scans were cross-sectional. Therefore, it was difficult to say that older children and young adults tend to have new renal scarring. To the best of our knowledge, longitudinal studies using multiple DMSA scans from childhood to young adulthood in patients with SB have been quite rare. From a practical perspective, detecting the development of new renal scarring is more critical than evaluating the prevalence of old renal scarring. To investigate new renal scarring, longitudinal studies using DMSA scans are necessary. In our previous study in children aged >10 years with SB, VUR history was the most significant risk factor for DMSA abnormalities. Given these results, we hypothesized that individuals in their pre-teens and younger were more susceptible to renal cortical damage than teens and young adults. However, in the present longitudinal study, 18% of patients had DMSA abnormalities before age 12 years, and 21% of patients developed new DMSA abnormalities after age 13 years. Therefore, there was no definite age tendency for the development of new DMSA abnormalities from childhood to young adulthood. Strictly speaking, it was difficult to differentiate acquired renal scarring from congenital cortical loss such as renal hypoplasia, without a newborn baseline DMSA scan. In the present retrospective study, a baseline DMSA scan in the first year of life was not routinely performed. Therefore, the term “DMSA abnormality” was used instead of “renal
“scarring” in the present study. In the current EAU/ESPU guidelines, a DMSA scan, as a baseline evaluation in the first year of life, is recommended and could be repeated after recurrent febrile UTIs to define children who have scarring and are at risk. However, the vast majority of newborns and infants with SB have normal kidneys. Tanaka et al. reported that, from the data of the National Spina Bifida Patient Registry, in the 66 infants who underwent DMSA, no infant had both kidneys affected, and only 5 (7.6%) had one kidney affected. In addition, not all follow-up centers of SB children were able to perform DMSA scans. Cascio et al. reported that abnormalities were noted on 4 (6%) of the 68 baseline DMSAs performed in newborns with SB in the first year of life. Considering these facts and the high cost of the examination, the necessity of a baseline DMSA scan in infants with SB is uncertain.

The efficacy of surveillance DMSA scans in the follow-up of SB children was also uncertain. Although the data of the present study showed a constant increase of new DMSA abnormalities from childhood to young adulthood, these findings indicate neither the optimal time nor the appropriate frequency of follow-up DMSA scans. The EAU/ESPU guidelines recommend DMSA scans at the ages of 10 and 15 years if VUR was/is present or febrile UTI has occurred. To establish the protocol for selective use of DMSA scans in this group, evaluation of the risk factors for development of new
DMSA abnormalities was essential.

In the previous studies, the following were considered the risk factors for renal scarring: VUR/VUR history, bladder trabeculation, reduced bladder capacity, high MDP, febrile UTI, female sex, and the delayed initiation of CIC.(6-8, 14-16) However, the age range of the populations in each study was quite wide, and the characteristics of the populations were different. Sager et al. analyzed 60 children with MMC aged less than 1 year who received CIC in the first days of life.(16) On the other hand, Ottolini et al. investigated 207 patients aged 1 to 30 years treated with CIC for a mean duration of 6.6 years.(6) To the best of our knowledge, there has been no study comparing the risk factors for renal scarring in different stages of child development with SB.

In the present study, the possible risk factors for new DMSA abnormalities were investigated in the same children in two different growth stages (age ≤12 years, age ≥13 years). In childhood (age ≤12 years), MDP was significantly higher in the abnormal DMSA group on univariate analysis, and three VUDS parameters (MDP, VUR, and bladder trabeculation) were identified as factors related to DMSA abnormalities on logistic LASSO regression analysis. However, in young adulthood (age ≥13 years), only VUR was identified as related on logistic LASSO regression analysis. Therefore, unfavorable VUDS findings except VUR are more critical with respect to predicting
DMSA abnormalities in childhood compared with young adulthood.

There are several limitations to this study other than the relatively small sample size and the retrospective nature of the study. First, a major drawback of this study was that febrile urinary tract infection was not thoroughly investigated. In our previous study, a history of febrile urinary tract infections was a significant risk factor for renal scarring, as in other studies. To prevent new renal scarring, early detection and treatment of febrile UTI is mandatory. However, the diagnosis of febrile UTI is not straightforward in this population on CIC because bacteriuria is extremely common. In addition, most episodes of febrile UTI are likely treated in local clinics without precise bacteriological examinations and renal imaging, making the exact history of febrile UTI unclear in regular visits at our institution. Furthermore, although febrile UTI is the key symptom of acute pyelonephritis, new renal scarring was recognized without definite febrile UTI episodes in SB children on CIC. Ottorini et al. reported that 26% of new renal scars were not preceded by documented febrile UTI episodes. Second, DMSA scans and VUDS were not always performed at the same age (Table 1). Therefore, the data of urodynamic variables potentially differed at the time of DMSA.

Third, as stated previously, most children did not undergo baseline DMSA in infancy. Therefore, congenital renal cortical loss was not differentiated from new renal scarring in
the evaluation of children (age ≤12 years). Fourth, routine DMSA scans were performed every 6 years. Thus, there was a degree of detection bias for DMSA abnormalities when using Kaplan-Meier survival curves in the present study.

Fifth, the effects of anticholinergics on VUDS variables were not assessed, although anticholinergics can change bladder characteristics. Last, bowel function and bowel regimens, which might affect the risk of UTIs, potentially affecting the development of renal scarring, were not investigated in the study population.
CONCLUSIONS

In children with SB using CIC, there was no definite age tendency in the development of new DMSA abnormalities. In the present longitudinal study, 18% of the patients had DMSA abnormalities before age 12 years, and 21% of patients developed new DMSA abnormalities after age 13 years. With respect to factors related to DMSA abnormalities, there were differences between childhood and young adulthood. Although VUR was related to new DMSA abnormalities in both periods, other VUDS parameters including MDP and bladder trabeculations were related to new DMSA abnormalities only in childhood.
References


Figures

Figure 1
Kaplan-Meier curves for patients free of DMSA abnormalities

Supplementary Files
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- final20221227Table1.docx
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