Acta Medica et Biologica
Vol. 40, (Suppl.) 11-16, 1992

Reflux Nephropathy and Lower Urinary Tract Function in Patients with Spina Bifida

Hitoshi TAKAHASHI, Akihiko HATANO, Kenji OBARA, Masayuki TAKEDA, Yasushi KATAYAMA, Toshiki TSUTSUI and Shotaro SATO

Department of Urology, Niigata University School of Medicine, Asahi-machi 1, Niigata City, Niigata 951, Japan

Summary. **Vesicoureteral reflux, pyelonephritis, a low compliance bladder, and urethral overactivity are thought to be risk factors for renal deterioration in patients with spina bifida. We studied the relationship between these factors and renal function as shown by intravenous pyelography or ^{99m}Tc-dimercaptosuccinic acid (DMSA) renal uptake in spina bifida patients. All four factors were found to be related to upper tract deterioration, and especially reflux was closely related to renal function.**

In addition, we studied the changes of filling cystometry parameters after antireflux surgery in spina bifida patients with secondary reflux. After antireflux surgery, the bladder capacity, maximum resting pressure, and bladder compliance all changed, and in patients who had grade 4 or 5 reflux, the changes were quite marked.

INTRODUCTION

Renal function in patients with primary vesicoureteral reflux (VUR) is closely related to the grade of reflux[1] or the presence of urinary tract infection (UTI). On the other hand, renal function in patients with secondary VUR due to neurogenic bladder is largely influenced by the function of the lower urinary tract.[2-7] VUR, pyelonephritis, a low-compliance bladder, and urethral overactivity are generally considered to be the risk factors for renal deterioration in patients with spina bifida. We studied the relationship between these factors and the results of intravenous pyelography (IVP) or ^{99m}Tc-dimercaptosuccinic acid (DMSA) renal uptake scanning in patients with spina bifida. In addition, we investigated the changes in filling cystometry parameters following antireflux surgery in spina bifida patients with secondary VUR.

PATIENTS AND METHODS

From 1983 to July 1991, 93 patients with spina bifida underwent urinalysis and IVP. Of these 93 patients, retrograde cystography was performed in 63, filling cystometry in 69, and filling cystometry with anal sphincter electromyography in 33. ^{99m}Tc-DMSA renal scintigraphy was also performed in 50 patients. A total of 186 renal units were analyzed.

The hydronephrosis or clubbing of the renal calyces was defined as an abnormal IVP, and the renal uptake of ^{99m}Tc-DMSA was adjusted for its known age-related decrease (renal ^{99m}Tc-DMSA uptake/ normal uptake).[8] VUR was graded according to the international classification.[9] In addition, UTI was classified as follows: grade 0, no infection; grade 1, cystitis only; and grade 3, pyelonephritis.

Filling water cystometry (20-30 ml/min) was performed in the supine position using an indwelling urethral catheter with an 8-16 F diameter and 2-3 lumens. Bladder compliance was calculated by dividing the volume change by the change in detrusor pressure just before a strong desire to void or at the time of leakage of urine from the urethral meatus (maximum resting pressure).[10] Low compliance was defined as a level less than 10 ml/cmH_2O. Simultaneous electromyographic tracings were obtained by plate electrode from the anal sphincter, which substitutes for the dysfunctional external urethral sphincter in these patients.

For statistical analysis, the chi-squared test or Fisher's exact test was used to compare the factors related to renal deterioration with the IVP findings. For comparing these factors with the renal ^{99m}Tc-DMSA uptake/normal uptake ratio (renal uptake ratio), Wilcoxon's rank-sum test was used.

We also studied the changes of filling cystometry

parameters after antireflux procedures in 7 patients with spina bifida. The grade of VUR was classified before and after seygery as described. All postoperative cystometry was done at 3-6 months after surgery. For statistical analysis, Wilcoxon's signed-rank test was used to compare the bladder capacity, maximum resting pressure, and bladder compliance after the antireflux procedure with those before surgery.

RESULTS

A) Relationship between IVP and renal uptake ratio

One hundred renal units were evaluated in this study. The renal uptake ratio was 1.02 ± 0.21 for subjects with normal IVP findings, while that of those with an abnormal IVP was 0.74 ± 0.38. There was a significant difference between the two groups ($p < 0.01$).

B) Relationship between VUR and renal deterioration

Eighteen of the 92 (19.6%) renal units without VUR had abnormal IVP findings, while 25/34 (73.5%) units with VUR did so. There was a significant difference between these groups ($p < 0.01$).

The renal uptake ratio for ^{99m}Tc-DMSA was 0.99 ± 0.27 for subjects without VUR, 0.76 ± 0.34 for those with VUR, 0.89 ± 0.39 with grade 1-3, and 0.63 ± 0.30 with grade 4-5 VUR. It showed significant differences between patients with and without VUR, and between those with grade 1-3 and grade 4-5 VUR ($p < 0.01$ and $p < 0.05$).

C) Relationship between VUR and other factors promoting renal deterioration

Only 13/92 (14.1%) patients without VUR had pyelonephritis, while 20/34 (58.8%) with VUR had this complication ($p < 0.01$).

Twenty-six out of 79 (32.9%) patients without VUR had a low-complicane bladder, while 17/29 (58.6%) with VUR had one. ($p < 0.05$). Finally, Only 9/40 (22.5%) patients without VUR had urethral overactivity, while 9/13 (69.2%) with VUR had an overactive urethra ($p < 0.05$).

D) Relationship between UTI and renal deterioration

Twenty-six out of 153 (17.0%) renal units without pyelonephritis had abnormal IVP findings, while 22/33 (66.7%) with pyelonephritis had IVP abnormalities. ($p < 0.01$).

The renal uptake ratio for ^{99m}Tc-DMSA was 0.94 ± 0.16 for subjicts with grade 0,0.95 ± 0.31 for those with grade 1, and 0.80 ± 0.42 with grade 2 UTI. It showed no significant difference in relation to UTI grade.

E) Relationship between lower urinary tract function and renal deterioration

Eighteen out of 88 (20.5%) renal units with normal compliance had abnormal IVP findings, while 21/50(42%) with low compliance had IVP abnormalities ($p < 0.05$).

The renal uptake ratio for ^{99m}Tc-DMSA was 0.99 ± 0.31 for subjects with normal compliance and 0.91 ± 0.33 with a low-compliance bladder. It showed no relation to bladder compliance.

Three out of 48 (6.25%) renal units with an incompetent urethra had abnormal IVP findings, while 13/18 (72.2%) with urethral overactivity had IVP changes ($p < 0.01$).

The renal uptake ratio for ^{99m}Tc-DMSA was 0.99 ± 0.19 for subjects with an incompetent urethra and 0.71 ± 0.41 with urethral overactivity. It had relation to urethral function ($p < 0.05$).

F) Cystometry parameters before and after antireflux surgery

The patients who underwent antireflux surgery included 3 males and 4 females. Three patients had bilateral VUR, 2 had left-sides reflux, and 2 had reflux on the right. Of the renal units with VUR, 1 was grade 1, 4 were grade 3, 1 was grade 4, and 4 were grade 5. Six out of 10 ureters had a Pollitano-Leadbetter repair, 2 had a Glenn-Anderson repair, and 2 had a Paquin's repair. Refluxes disappeared after the operation in all cases (Table. 1).

After antireflux surgery, the bladder capacity decreased (from 308 ± 136 to 265.7 ± 99.3 ml, $p < 0.01$), the maximum resting pressure increased (from 16.6 ± 7.34 to 32.4 ± 21.2 cmH_2O, p=NS), and the bladder compliance decreased significantly (from 26.48 ± 23.2 to 11.0 ± 5.4 ml/cmH_2O, $p < 0.025$). In the patients who had grade 4 or 5 VUR, the changes were more marked (Fig. 1).

Two patients in whom the parameters changed markedly are presented briefly.

Case 5 was a 16-year-old girl with left grade 3 and right grade 4 VUR. H_2O filling cystometry showed a maximum bladder volume of 600 ml, a maximum

Table 1. Cystometry parameters before and after antireflux surgery in 7 patients with spina bifida

Case	Sex	Age	Disease	VUR side		Preoperative			Postoperative		
				(LT)	(RT)	Vol. (ml)	Press. (cmH_2O)	Comp. (ml/cmH_2O)	Vol.	Press.	Comp.
*1.	f	14	MMC	5	5	300	29	10.3	150	22	6.8
2.	m	19	SBO	0	1	400	18	22.2	320	18	17.8
3.	m	9	SBO	0	3	200	18	11.1	170	15	11.3
4.	f	11	MMC	3	0	240	3	80.0	420	25	16.8
*5.	f	16	SBO	3	4	600	18	33.3	320	42	7.6
6.	m	16	MMC	3	0	220	12	18.3	330	22	15.0
*7.	f	9	SBO	5	5	200	20	10.0	150	80	1.9

vol.=bladder volume, press.=maximum resting pressure, comp=bladder compliance, MMC=myelomeningocele, SBO=spina bifida oculta
*High grade VUR (≧grade 4)

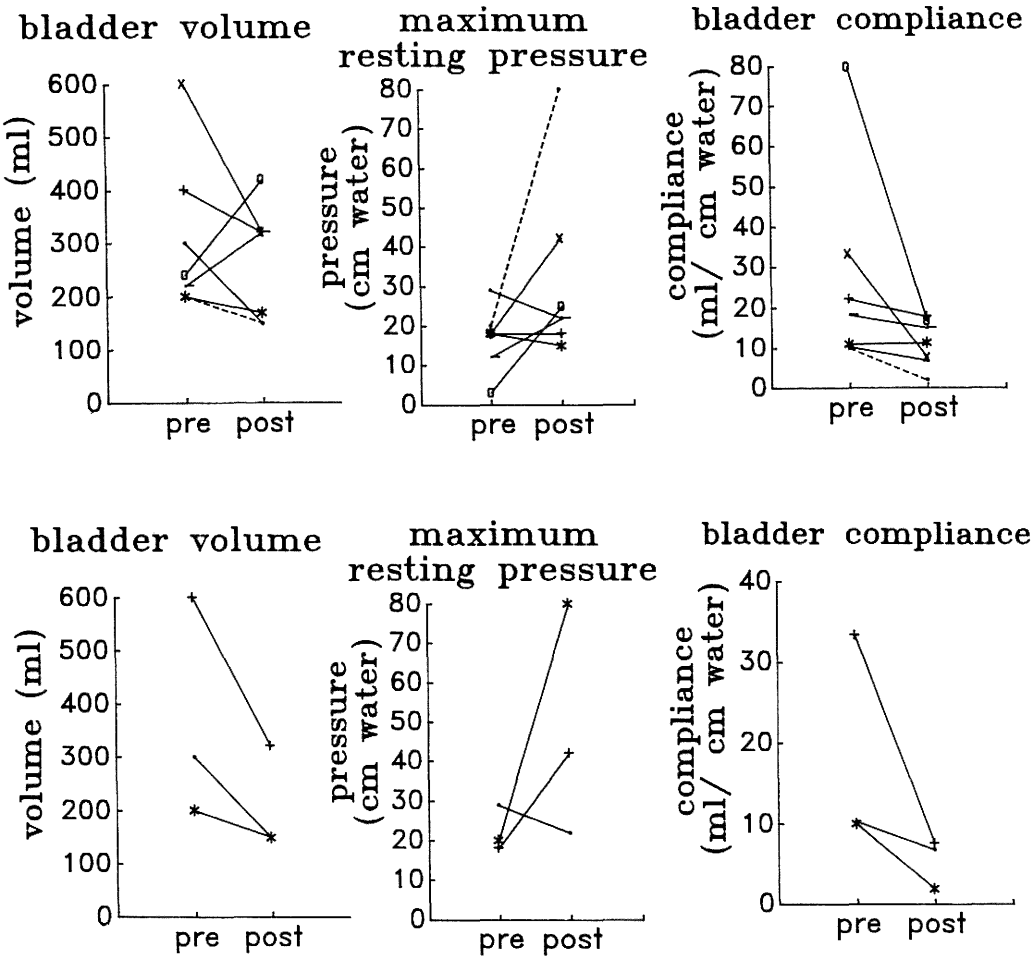

Fig. 1. *Top*: Urodynamic studies before and after antireflux surgery in patients with spina bifida. *Bottom*: In the patients who had grade 4 or 5 VUR, the changes were more marked.

bladder resting pressure of 18 cmH_2O, and a bladder compliance of 33.3 ml/cmH_2O before operation. These parameters changed to 320 ml, 42 cmH_2O and 7.6 ml/cmH_2O after the operation. In this patient, the frequency of abdominal distension on filling of the bladder with urine was increased. However, she performed clean intermittent self-catheterization at a bladder volume of about 200 ml; her BUN and serum creatinine levels remained stationary and she had no urinary incontinence (Fig. 2).

Case 7 was a 9-year-old girl who had bilateral grade 5 VUR. H_2O filling cystometry showed a maximum bladder volume of 200 ml, a maximum bladder resting pressure of 20 cmH_2O, and bladder compliance of 10 ml/cmH_2O before operation. Although she was controlled by clean intermittent self-catheterization after the operation, her BUN and serum creatinine increased gradually. At 3 months after the operation, the BUN level increased from 27 to 47 mg/dl, and the serum creatinine from 1.2 to 2.1 ml/dl. She was then

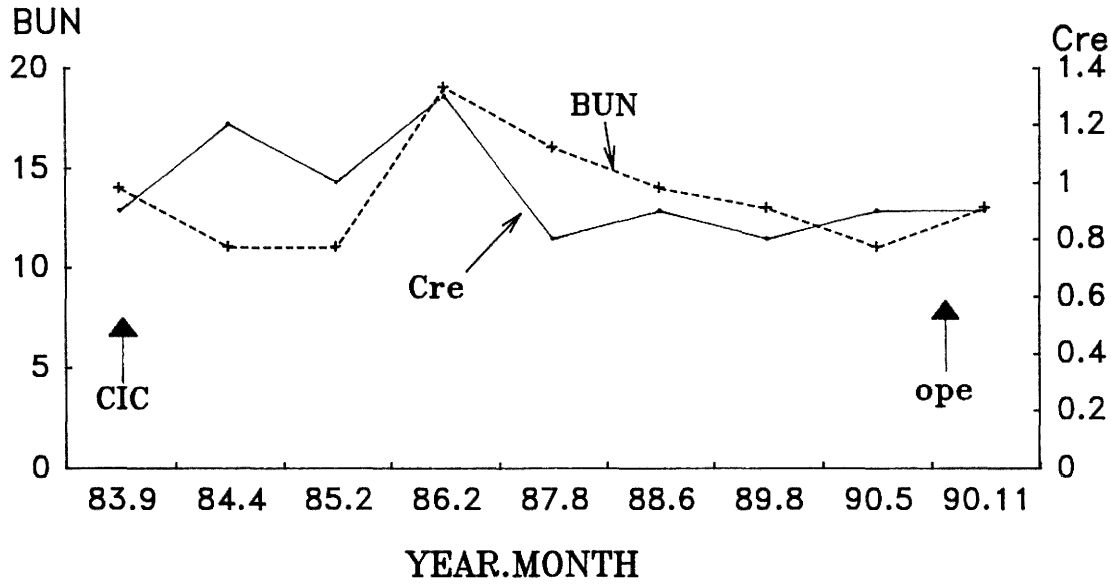

Fig. 2. Changes of BUN and serum creatinine (Cre) levels in Case 5. In this patient, the cystometry parameters deteriorated, but the BUN and serum creatinine levels did not change after the antireflux procedure.

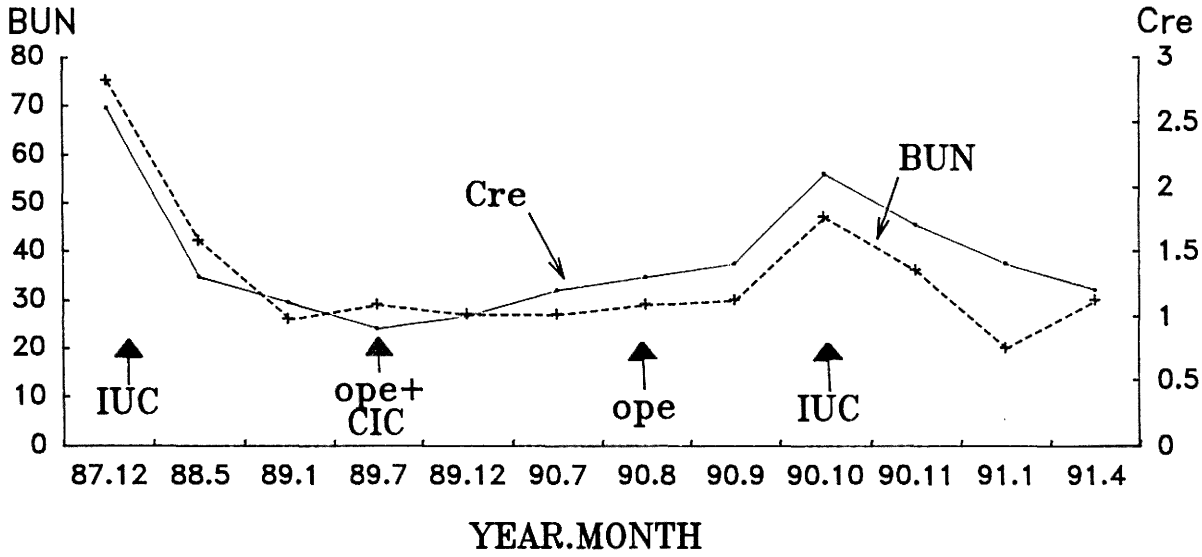

Fig. 3. Changes of BUN and serun creatinine (Cre) levels in Case 7. In this patient, the BUN and serum creatinine levels became worse after the antireflux along with deterioration of the cystometry parameters.

treated by indwelling urethral catheterization. At that time, H_2O filling cystometry showed a maximum bladder volume of 150 ml, a maximum bladder pressure of 80 cmH_2O, and a bladder compliance of 1.9 ml/cmH_2O. She is now controlled by daytime self-catheterization and an indwelling catheter at night; the BUN and serum creatinine levels are 30 and 1.2 mg/dl, respectively (Fig. 3).

DISCUSSION

In patients with a neurogenic bladder, not only VUR but also lower urinary tract dysfunction may affect renal function. VUR and associated pyelonephritis may both contribute to reflux nephropathy. In addition, it is possidle that increased bladder pressure due to functional obstruction of the lower urinary tract may cause renal deterioration in these patients.[2-7]

The frequency of deterioration of the upper urinary tract in patients with spina bifida is 11-41%[5,7,9,12,13] and VUR occurs in 25-45%.[9,11-13] Our levels of 25.8% for upper urinary tract damage and 27.0% for VUR were thus within the range of these other reports.

The grade of VUR is reported to be related to upper urinary deterioration on IVP films and to ^{99m}Tc-DMSA renal uptake.[1,13] In our series, 18 (19.6%) of 92 subjects without VUR had changes of the upper urinary tract. This suggested that not all renal damage in spina bifida is due to VUR and that renal damage due to functional lower urinary tract obstruction may also occur. However, the relationship between VUR and ^{99m}Tc-DMSA demonstrated that reflux was the more important factor contributing to renal damage in spina bifida.

The UTI grade was related to upper tract deterioration on IVP, but was not correlated with DMSA uptake. This may have been contributed to by problems with the grading method such as its retrospective nature and assigning grade 3 to all cases.

Scott[14] reported that the median bladder compliance of patients with an abnormal upper urinary tract was 9 ml/cmH_2O. Although the normal bladder compliance has not actually been defined,[10] we used 10 ml/cmH_2O as the cutoff value. Both a low-compliance bladder and an overactive sphincter promoted renal deterioration, as was noted in previous reports.[2-7] However, IVP findings were more related to renal deterioration than DMSA uptake. DMSA uptake is mainly related to renal function, while the IVP shows renal function and dilatation of the upper urinary tract, and this is probably why a discrepancy between these imaging methods was noted.

Bladder comliance decreased in some patients after operation, and this is why bladder compliance had little relation to renal function by DMSA uptake before operations. Even when bladder compliance was high on filling cystometry before the antireflux procedure, the value determined was affected by not only bladder function but also leakage to the upper urinary tract due to VUR.[15] However, if VUR disappeared after surgery, filling cystometry then showed the function of the bladder itself and this is why a decrease of compliance was sometimes noted. Such a change of bladder compliance may further damage renal function in some patients, as shown in our case 5.

In conclusion, VUR, pyelonephritis, low compliance bladder, and urethral overactivity causes the upper urinary tract damage, especially VUR has close relation to renal function. However, in patients with spina bifida, the obstruction by lower urinary tract dysfunction affects upper urinary tracts too. We emphasize that not only a treatment of VUR but also urinary control is important in these cases.

Acknowledgements: We are greatly indebted to Dr. Ryuuji Takaki (head of the Department of Urology at Niigata Rosai Hospital) for his helpful advice.

REFERENCES

1) Takeda M: Renal function evaluation with ^{99m}Tc-DMSA renal uptake in primary vesico-ureteral reflux patients. *Jap J Urol* **79**: 126-135, 1988.
2) Diokno A C, Kass E, Lapides J: New approach to myelodysplasia. *J Urol* **116**: 771-772, 1976.
3) Bauer S B, Labib K B, Dieppa R A, Retik A B: Urodynamic evaluation of boy with myelodysplasia and incontinence. *Urology* **10**: 354-362, 1977.
4) McGuire E J, Woodside J R, Borden T A, Weiss R M: Prognostic value of urodynamic testing in myelodysplastic patients. *J Urol* **126**: 205-209, 1981.
5) Noto H, Harada, T, Nisizawa O, Morita T, Tsuchida S, Kimura Y: Urological managements and the results of the patients with congenital neurogenic bladder due to spina bifida—with special reference to the urodynamic evaluation of the lower urinary tract infection. *Jap J Urol* **74**: 994-1002, 1983.
6) Side A A, Dykstra D D Gonzalez R: The value of urodynamic testing in the management of neonates with myelodysplasia: A prospective study. *J Urol* **135**: 90-93, 1986.

7) Brem A S, Martin D, Callaghan J, Maynard J: Long-term renal risk factors in children with meningomyelocele. *J Pediat* **110**: 51-55, 1987.
8) Takeda M: Studies on the evaluation of renal function in urological renal disorders with ^{99m}Tc-DMSA renal uptake. 1. Change with age. *Jap J Urol* **78**: 1553-1558, 1987.
9) International Reflux Study Committee: Medical versus surgical treatment of primary vesicoureteral reflux in children. *J Urol* **125**: 277, 1981.
10) International Continence Society Committee on Standardization of Terminology: The standardization of terminology of lower urinary tract function. *Scand J Urol Nephrol* **114**: 5-19 (Suppl), 1988.
11) Scheriter F: Managenent of meningomyelocele. *Akt Urol* **21**: 123-128 (suppl), 1990.
12) Takaki R: Urological complications associated with spina bifida and their managements: A clinical study. *Jap J Urol* **69**: 448-458, 1978.
13) Konda R, Orikasa S, Nakamichi G: Studies on reflux nephropathy II: Evaluation of renal function by ^{99m}Tc-DMSA renal scintigraphy. *Jap J Urol* **75**: 1602-1610, 1984.
14) Scott M A, Abras P: Bladder compliance in patients with spina bifida: *Nerourol Urodyn* **6**: 232, 1989 (Abstract).
15) Woodside J R, Borden T A: Determination of true intravesical filling pressure in patients with vesicorueteral reflux by Fogarty catheter occlusion of ureters. *J Urol* **127**: 1149-1152, 1982.