

Role of plasma renin activity in the management of primary vesicoureteric reflux: A preliminary report

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Background. Nonoperative management is the choice of therapy in most patients with primary vesicoureteric reflux (VUR). Such patients are regularly monitored for breakthrough urinary tract infection, deterioration of renal function, and progression/appearance of new scars as the indicators for switching over to surgical intervention. In this descriptive study, we report our additional observations on serial measurement of plasma renin activity (PRA) in a group of such children followed prospectively.

Methods. Twenty-six children (16 males and 10 females) with various grades (grades I to V) of primary VUR were enrolled. Besides the conventional investigations, we also monitored PRA. Ureteric reimplantation was performed based on established international criteria. PRA levels were correlated with the need for surgical intervention retrospectively.

Results. Mean age at presentation was 39.3 months (range, 12 to 120 months). Nineteen children (73%) were subjected to ureteric reimplantation. The mean PRA in this group ($N = 19$) was 6.97 ng/mL/hour versus 3.28 ng/mL/hour in patients who were continued on nonoperative management ($N = 7$). Postoperatively, the PRA reduced and stabilized in all 18 patients at a mean value of 5.4 ng/mL/hour.

Conclusion. The currently accepted end points of medical management are inconsistent. On the other hand, 94.7% of children in the surgical group had shown an activation and a progressive increase in PRA. Postoperatively, the PRA was reduced and stabilized in all these patients. Our preliminary observations suggest that high PRA is a more sensitive indicator for surgical intervention as compared to the existing criteria.

Role of plasma renin activity (PRA) in monitoring the nonoperative management of primary vesicoureteric reflux (VUR) has not been studied in the past. Although nonoperative management is the choice of therapy in most patients, surgery is undertaken if children develop

an increase in the grade of reflux and scar, decline in split renal function (SRF), rise in serum creatinine, decline in glomerular filtration rate (GFR), and recurrent breakthrough urinary tract infection. In this descriptive study, we report our observations in a group of such children followed prospectively by serial measurement of PRA.

METHODS

Twenty-six children (16 males and 10 females) with various grades (grades I to V) of primary VUR were enrolled for the study in the Pediatric Urology Clinic of the All India Institute of Medical Sciences, New Delhi, India. We monitored PRA, renal scars, SRF, GFR, serum creatinine, blood pressure and episodes of breakthrough urinary tract infections at regular intervals. PRA was measured by radioimmunoassay using commercially available kit SB REN-2 (Diagnostic Products, Los Angeles, CA, USA).

Normal PRA from the laboratory were 1 to 12 months = 4 to 8 ng/mL/hour; 1 to 3 years = 1 to 9 ng/mL/hour; 3 to 6 years = 1 to 5 ng/mL/hour; 6 to 15 years = 1.4 to 2.6 ng/mL/hour; 15 to 18 years = less than 4.3 ng/mL/hour. Renal scars were studied using technetium-99m 2,3-dimercaptosuccinic acid (DMSA) scans and were graded (1 to 4) according to the grading system of Smellie et al [1]. Grade of reflux was recorded by micturating cystourethrogram (MCU) using the international criteria (grades I to V) and SRF was measured by L,L ethylmethyl cysteine (LLEC) radionuclide study. GFR was measured by multiple blood sampling technique following diethylenetetraaminopentaacetic acid (DTPA) injection. Percentage change in GFR was calculated by the formula adopted by Smellie et al [2] $(\text{final GFR} - \text{initial GFR} / \text{initial GFR} \times 100)$. Children developing increase in scar grades, decline in SRF, rise in serum creatinine, decline in GFR, and recurrent breakthrough urinary tract infections were identified. Ureteric reimplantation was performed based on established international criteria. PRA

Key words: vesicoureteric reflux, renin, renal scars, ureteric reimplantation, congenital uropathy; reflux nephropathy.

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Table 1. Outcome of patients with grade II reflux in the present series

Serial number	VUR grade R/L		SRF% R/L		Scars R/L		Creatinine	GFR	PRA	Surgery	Follow-up months	Creatinine	Blood pressure
	Age/gender	Follow-up months	I	F	I	F	I/preop	I/F	I/F			F	I/F
1	II/I 60 M	24	52/48	51/49	1/0	1/0	0.6/0.8	68.7/89.0	3.8/3.2	N	3.6	0.8	108/76; 100/80
2	II/I 36 F	36	Rt. NFK	Rt. NFK	4/0	4/0	0.7/0.9	68.0/55.5	3.8/6.8	Rt. Nx	5.6	1.0	110/80; 108/80
3	I/II 72 M	24	54/46	52/48	0/1	0/1	0.6/0.7	106.7/108.0	2.6/2.9	N	3.0	0.7	104/72; 100/70
4	II/II 48 F	36	49/51	52/48	0/0	0/0	0.7/0.8	90.1/108.0	3.5/2.6	N	2.8	0.8	100/68; 98/64

Abbreviations are: VUR, vesicoureteric reflux; M, male; F, female; I, initial value; preop, value just before surgery; F, final value; NFK, nonfunctioning kidney; Nx, nephrectomy; SRF, split renal function; R, right side; L, left side; GFR, glomerular filtration rate; PRA, plasma renin activity expressed in ng/mL; Y, surgery done; N, no surgery done.

Table 2. Outcome of patients with grade III reflux in the present series

Serial number	VUR Grade R/L		SRF% R/L		Scars R/L		Creatinine	GFR	PRA	Surgery	Follow-up months	Creatinine	Blood pressure
	Age/gender	Follow-up months	I	F	I	F	I/preop	I/F	I/F			F	I/F
1	0/III 36 M	28	80/20	82/18	0/4	0/4	0.8/0.9	52/48	3.8/7.9	Y	5.9	0.8	120/80; 118/80
2	III/III 48 F	36	62/38	66/34	1/3	1/3	0.8/0.8	70/62	3.0/6.2	Y	6.0	0.8	116/78; 114/82
3	III/0 24 M	30	32/64	28/72	2/0	3/0	0.7/0.7	78/80	3.2/3.8	N	3.2	0.7	114/82; 116/80
4	II/III 32 M	24	42/58	48/52	2/1	2/1	0.6/0.7	89/94	3.8/3.5	N	3.9	0.7	106/76; 108/80
5	III/0 120 M	28	42/58	40/60	1/0	1/0	0.7/0.8	98/106	3.2/3.8	N	3.6	0.8	108/74; 106/76
6	III/III 48 F	26	49/51	48/52	2/2	2/2	0.8/0.9	92/90	3.9/5.8	Y	4.6	0.9	120/90; 108/70
7	III/III 60 M	24	48/52	49/51	2/1	2/1	0.8/0.8	100/98	2.6/3.2	N	2.9	0.8	108/72; 110/70

Abbreviations are: M, male; F, female; I, initial value; preop, value just before surgery; F, final value; NFK, nonfunctioning kidney; Nx, nephrectomy; SRF, split renal function; R, right side; L, left side; GFR, glomerular filtration rate; PRA, plasma renin activity expressed in ng/mL; Y, surgery done; N, no surgery done.

was correlated with the need for surgical intervention retrospectively.

In this descriptive study, we have used proportion to summarize qualitative variable. As the number of patients are small, no statistical inference in the form of *P* value is computed. In this pilot study, in addition to proportions, we have also provided the raw data for the benefit of readers for an understanding at the patient level.

RESULTS

Twenty-six children (16 males and 10 females) were enrolled in the study. Mean age at presentation was 39.3 months (range, 13 to 120 months). Nineteen children (73%) were subjected to surgical intervention. As a policy, these patients underwent bilateral Cohen’s ureteric reimplantation, even when the reflux was unilateral. The distribution of patients with various grades of reflux is indicated in Tables 1 to 4. Nine out of 26 patients showed a progression in scar grade (Table 5), two out of 26 showed a fall in SRF of more or equal to 5%, 11 out of 26 children had serum creatinine levels higher than the upper limit for the age, eight out of 26 children were

detected to have hypertension, and two out of 26 had breakthrough urinary tract infections (more than two episodes/6 months) warranting surgery. Significant fall in GFR (>10 mL/min/1.7 m²) was seen only in two out of 26 patients. All children in the surgical group, except one (18 out of 19) (94.7%), had shown an activation and a progressive increase in PRA. The mean PRA in this group (*N* = 19) was 6.97 ng/mL/hour versus 3.28 ng/mL/hour in patients who were continued on nonoperative management (*N* = 7). Postoperatively, the PRA was reduced and stabilized in all 18 patients at a mean value of 5.4 ng/mL/hour, which was higher than normal. Five out of eight patients had normalization of their blood pressure. Only one patient in the surgical group with PRA within the normal range had presented with bilateral grade V reflux with nephropathy (four of four scars) and chronic renal failure (CRF) (creatinine 5.6 mg/dL, GFR 20 mL/min/1.73 m²). This child had breakthrough urinary tract infections (three episodes in a 6-month period), a falling GFR, and was subjected to bilateral ureteric reimplantation. Postoperatively, he is free of urinary tract infections, but continues in CRF, hyperten-

Table 3. Outcome of patients with grade IV reflux in the present series

Serial number	VUR Grade R/L		SRF% R/L		Scars R/L		Creatinine		GFR		PRA		Surgery	Follow-up months	Creatinine F	Blood pressure I/F
	Age/gender	Follow-up months	I	F	I	F	I/preop	I/F	I/F	I/F						
1	III/IV 13 M	32	52/48	56/44	1/3	1/4	0.8/0.9	60/58	4.8/6.3	Y	6.2	0.8	128/90; 120/86			
2	I/IV 16 F	36	68/32	72/28	0/3	0/4	0.9/1.1	58/56	6.2/7.3	Y	6.5	1.1	110/80; 120/80			
3	IV/IV 20 M	28	51/49	54/46	1/2	1/3	0.8/0.9	98/92	2.2/6.8	Y	5.0	0.8	110/74; 108/70			
4	III/IV 18 M	30	62/38	60/40	1/2	1/2	0.9/0.9	70/62	3.0/6.2	Y	5.6	0.9	108/72; 110/70			
5	III/IV 28 F	36	58/42	60/40	2/3	2/3	0.7/0.9	60/58	2.6/5.7	Y	3.2	0.8	128/89; 118/80			
6	I/IV 30 F	36	65/35	70/30	0/3	0/3	0.6/0.8	98/89	3.8/6.8	Y	6.2	0.8	118/76; 120/80			
7	II/IV 12 M	28	70/30	72/28	1/4	1/4	0.8/1.1	78/76	3.2/7.42	Y	3.6	0.9	108/72; 118/70			
8	III/IV 16 F	28	58/42	56/44	2/3	2/3	0.7/0.9	75/68	3.0/5.9	Y	4.6	0.8	118/82; 118/80			

Abbreviations are: M, male; F, female; I, initial value; preop, value just before surgery; F, final value; NFK, nonfunctioning kidney; Nx, nephrectomy; SRF, split renal function; R, right side; L, left side; GFR, glomerular filtration rate; PRA, plasma renin activity expressed in ng/mL; Y, surgery done; N, no surgery done.

Table 4. Outcome of patients with grade V reflux in the present series

Serial number	VUR Grade R/L		SRF% R/L		Scars		Creatinine		GFR		PRA		Surgery	Follow-up months	Creatinine F	Blood pressure I/F
	Age/gender	Follow-up months	I	F	I	F	I/preop	I/F	I/F	I/F						
1	III/V 36 M	24	68/32	72/28	1/4	1/4	0.9/1.1	58/49	3.6/5.7	Y	5.6	1.0	118/76; 120/80			
2	V/V 48 F	18	34/66	30/70	4/4	4/4	3.0/2.8	17.4/15.4	5.8/13.3	Y	10.8	2.2	132/90; 130/80			
3	V/V 60 F	12	40/60	42/58	3/4	4/4	1.8/1.7	38/28	4.0/6.2	Y	5.0	1.5	126/90; 118/76			
4	V/V 36 F	12	82/18	90/10	1/4	2/4	1.2/1.3	66/35	6.14/13.9	Y	10.0	1.4	128/89; 120/88			
5	III/V 28 M	18	60/40	62/38	1/3	1/3	0.9/1.1	68/65	2.45/7.68	Y	3.6	1.0	118/74; 112/76			
6	V/V 32 M	17	90/10	88/12	3/4	4/4	4.5/5.6	25/20	2.4/2.6	Y	2.1	5.8	140/100; 142/100			
7	IV/V 46 F	12	Lt. Poor fn.		4/4	4/4	3.0/3.8	35/18	3.6/4.1	Y	2.8	2.6	138/92; 140/90			

Abbreviations are: M, male; F, female; I, initial value; preop, value just before surgery; F, final value; NFK, nonfunctioning kidney; Nx, nephrectomy; SRF, split renal function; R, right side; L, left side; GFR, glomerular filtration rate; PRA, plasma renin activity expressed in ng/ml; Y, surgery done; N, no surgery done.

Table 5. The association of various indications for surgery vis-a-vis plasma renin activity (PRA) in patients who required ureteric reimplantation (out of 26 patients initially managed nonoperatively, 19 required surgery) (73%)

Indications for surgery	Progression of scars N = 9	Fall in SRF N = 2	Rise in creatinine N = 11	PRA 4.0 ng/mL N = 18	High blood pressure N = 8	^a Episodes of UTI N = 2	Fall in GFR N = 6
Percentage association	47.3	10.5	57.9	94.7	42.1	10.5	31.5

Abbreviations are: SRF, split renal function; PRA, plasma renin activity; UTI, urinary tract infection (^amore than two episodes of breakthrough UTIs in 6 months were considered significant); GFR, glomerular filtration rate.

sion, and a low PRA. None of the other patients in the surgical group had any significant deterioration of renal function during the mean follow-up of 26.2 months (range, 12 to 36 months).

DISCUSSION

Traditionally, children with primary VUR and stable renal function are managed nonoperatively with the ex-

pectation of spontaneous resolution with age. Although the present criteria for surgical intervention are widely accepted, yet, the long-term safety of continued non-operative management has constantly been under scrutiny [3].

The currently accepted end points of medical management are inconsistent as indicated by an analysis of the present series. Patients who underwent surgery had variable criteria (Tables 1 to 4) and none of them met all

the criteria for surgical intervention (Table 5). These criteria are also irreversible. On the other hand, all children in the surgical group except one (18 out of 19) (94.7%) had shown an activation and a progressive increase in PRA. The mean PRA in this group ($N = 19$) was 6.97 ng/mL/hour versus 3.28 ng/mL/hour in patients who were continued on nonoperative management ($N = 7$). Postoperatively, the PRA reduced and stabilized in all 18 patients at a mean value of 5.4 ng/mL/hour, which is higher than normal.

Since the presently accepted criteria for intervention are not present uniformly in all the patients requiring surgery, the safety of continued nonoperative management is questionable. This issue especially assumes significance since the existing criteria for surgery are irreversible. Although, in some other congenital uropathies, a nonoperative approach is currently the mainstay of treatment [4, 5], there is continued search for early markers for surgical intervention. Study of the activated renin-angiotensin system (RAS) is one such attempt [6, 7].

Children with persistent reflux but preserved renal parameters are managed conservatively with the expectation of spontaneous resolution with age. However, children with persistent reflux of moderate to higher grade (III, IV, or V) who apparently have stable GFR, SRF, and serum creatinine pose difficulty in management. Many authors advocate that surgical correction does not alter the outcome in children with severe bilateral VUR and bilateral nephropathy [2, 8]. Many such children end up with early hypertension, CRF, and even end-stage renal disease (ESRD). Arterial damage in the area of renal scarring presumably leads to segmental ischemia and renin-driven hypertension. Recently, several studies have shown that renal scarring with or without VUR leads to activation of RAS, atrial natriuretic peptide, aldosterone, catecholamines, and Na-K ATPase, which, in turn, are responsible for pediatric hypertension, elevated resting heart rate, and palpitation [9, 10]. Chronic activation of renin-angiotensin-aldosterone system (RAAS) is associated with adverse structural remodeling of right and left ventricles characterized by reparative (i.e., microscopic scars) and reactive (i.e., perivascular/interstitial) fibrosis, leading to increased cardiovascular mortality [11]. Some authors have speculated that the unique scar associated redistribution of renin may play a pathophysiologic role in the progression of renal disease, including progression of scars (formation of atubular glomeruli due to periglomerular sclerosis) [12, 13]. Elevated renin may be related to eventual hypertension for some patients, but others with high renin remain normotensive, while a small number revert to normal with extended follow-up [14]. In a 5-year prospective study, patients with long-standing reflux nephropathy were found to have a higher mean PRA [14] and even hyper-reninemic-

normotensive patients carry a 10% to 20% risk of developing hypertension. Identification of early activation of RAS is, therefore, important since PRA may prove to be of value in early identification of children at risk of developing hypertension [15].

Both sterile and infected urine is known to produce parenchymal damage in different situations [3]. Prevention of reflux-associated renal changes may offer some benefit in reducing the incidence of hypertension, progression of scars, and cardiovascular changes [16]. In our study, 69.2% of patients (18 out of 26) showed activation of RAS and escalating levels of PRA.

In the present series, more than 96% had reflux nephropathy, eight out of 26 (30.7%) patients were hypertensive (seven had raised PRA and one had CRF and normal PRA) and 11 out of 26 (42.3%) were hyperreninemic normotensive. All of them ($N = 19$) were subjected to surgery. Postoperative follow-up showed reduction and stabilization of PRA in all the operated patients (19 out of 19), albeit at a mean PRA of 5.41 ng/mL/hour, which was higher than normal. Five out of eight patients (62.5%) showed normalization of blood pressure. At a mean of 26.2 months follow-up, only 7.6% patients (two out of 26) continue to be hypertensive requiring minimal dose of anti-hypertensive medications. None of the patients complain of palpitation or any other cardiovascular symptom. Hyperreninemic normotensive patients ($N = 11$) are under follow-up and constitute a risk group for hypertension, proteinuria, and other systemic adverse effects of hyperreninemia.

Hypertension is related to the grade of reflux and the severity of scarring in most series, especially with bilateral involvement [17–19]. Higher scar grades (2.9/3.6 vs. 1.09/3.0), more bilateral nephropathy (100% vs. 63.6%), and higher mean PRA (7.9 ng/mL/hour vs 6.8 ng/mL/hour) were seen among the hypertensive group versus the normotensive group.

As this is a descriptive study, we recommend further prospective studies to establish the role of PRA as a more sensitive marker in monitoring the management of patients with primary VUR. The existing criteria, once attained, are irreversible. Subclinical urinary tract infections and high pressure sterile intrarenal reflux are proposed to be some of the factors that lead to progressive nephropathy in patients under adequate medical therapy [3, 20]. It is, therefore, imperative to establish a more sensitive marker, such as PRA, in order to decide the most appropriate time for surgical intervention in nonoperatively treated patients with VUR and to prevent the deleterious effects of RAAS activation.

Our results suggest that serial measurement of PRA may help in better stratification of patients with moderate to high grade (III, IV, and V) VUR and reflux nephropathy with respect to management and prognosis.

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REFERENCES

- SMELLIE J, EDWARDS D, HUNTER N, et al: Vesicoureteric reflux and renal scarring. *Kidney Int* 8:565-572, 1975
- SMELLIE J, BARRATT M, CHANTLER C, et al: Medical versus surgical treatment in children with severe bilateral vesico ureteric reflux and bilateral nephropathy: A randomised trial. *Lancet* 357:1329-1333, 2001
- HODSON J, MALING TMJ, ME MANAMON PJ, et al: The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). *Br J Radiol* (Suppl 13):S1-S26, 1975
- BAJPAI M, CHANDRASEKHARAM VVSS: Nonoperative management of neonatal moderate to severe bilateral hydronephrosis. *J Urol* 167:662-665, 2002
- ULMAN I, JAYANTHI VR, KOFF SA: The long term follow up of newborns with severe unilateral hydronephrosis initially treated nonoperatively. *J Urol* 164:1101-1105, 2000
- BAJPAI M, PURI A, TRIPATHI M, MAINI A: Prognostic significance of captopril renography for managing congenital unilateral hydronephrosis. *J Urol* 168:2158-2161, 2002
- HOMSY YL, TRIPP MB, LAMBERT R, et al: The captopril renogram: A new tool for diagnosis and predicting obstruction in childhood hydronephrosis. *J Urol* 160:1446-1449, 1998
- PIEPSY A, TAMMINEN-MOBIUS T, REINERS C, et al: Five-year study of medical or surgical treatment in children with severe vesico-ureteral reflux, dimercapto succinic acid findings. International Reflux Study Group in Europe. *Eur J Pediatr* 157:753-758, 1998
- PECO-ANTIC A, NOSTIC MINC D, BABIC D, et al: The captopril test an aid in the detection of scarring nephropathy as a cause of arterial hypertension in children. *Srp Arh Celok Lek* 127:305-311, 1999
- POMERANY A, KORYETS Z, REGEV A, et al: Is greater than normal nocturnal heart rate in children with renal scars a predictor of reflux nephropathy? *Blood Press Monit* 3:369-372, 1998
- CAMPBELL SE, JAMICHI JS, WEBER KT: Temporal differences in fibroblast proliferation and phenotype expression in response to chronic administration of angiotensin II or aldosterone. *J Mol Cell Cardiol* 27:1545-1560, 1995
- KONDA R, ONKASA S, SAKAI K, et al: The distribution of renin containing cells in scarred kidneys. *J Urol* 156:1450-1454, 1996
- CORREA-ROTTER R, HOSTETTER TH, MANNIVEL JC, et al: Renin expression in renal ablation. *Hypertension* 20:483-490, 1992
- SAVAGE JM, KOH CT, SHAH V, et al: Five year prospective study of plasma renin activity and blood pressure in patients with long standing reflux nephropathy. *Ach Dis Child* 62:678-682, 1987
- SAVAGE JM, DILLON MJ, SHAH V, et al: Renin and blood pressure in children with renal scarring and vesico-ureteric reflux. *Lancet* 26:441-444, 1978
- GOONASEKERA CD, DILLON MJ: Reflux nephropathy and hypertension. *J Hum Hypertens* 12:497-504, 1998
- TORRES VE, MALEK RS, SVENSSON JP: Vesicoureteric reflux in the adult: II. Nephropathy, hypertension and stones. *J Urol* 130:41-44, 1983
- WINTER AL, HARDY BE, ALTON DJ, et al: Acquired renal scars in children. *J Urol* 129:1190-1194, 1983
- HINCHLIFFE SA, CHAN YF, JONES H, et al: Renal hypoplasia and postnatally acquired cortical loss in children with vesicoureteric reflux. *Pediatr Nephrol* 6:439-444, 1992
- INTERNATIONAL REFLUX STUDY COMMITTEE: Medical versus surgical treatment of primary vesico ureteral reflux: A prospective international reflux study in children. *J Urol* 125:277-283, 1981