

Brief Reports

Primary Vesicoureteral Reflux: Progress of Disease, Somatic Growth and Renal Parameters

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Thirty children (45 units) in the age group 1 day-12 yrs with primary vesicoureteral reflux were studied prospectively and periodically assessed for renal function, scarring, grade of reflux and somatic growth parameters. Four children (6 units) with grade IV reflux underwent ureteric reimplantation. Complete resolution with medical management was seen in all 12 units of grade I-III reflux and in 5 of the remaining 27 units of grade IV-V reflux over 6 months-6 yrs. This group showed highly significant improvement in height ($p < 0.001$). The weight gain of the above 2 groups was statistically significant compared to those with persistent reflux. Focal defects were seen initially in 62% refluxing units. None of the patients showed deterioration in renal function or formation of new scars over the next 1-7 years. Three children on conservative management showed persistent growth retardation with associated breakthrough infection, hypertension, multiple renal scars and poor renal functional volume.

Key words: *Primary vesicoureteral reflux, Renal scarring, Somatic growth parameters, Urinary tract infection.*

Management of primary vesicoureteral reflux (VUR) is a controversial subject(1). Only a few studies have assessed the effect of the type of management on growth parameters (2,3). There is no controlled study on Indian children and we therefore prospectively observed the long-term effects of surgical and conservative treatment on renal status and somatic growth, especially in patients with severe VUR.

Subjects and Methods

All children with primary VUR attending our outpatient department between 1996-2003 were enrolled in the study. The baseline

investigations included urine for culture and sensitivity, blood pressure, micturating cystourethrogram (MCUG), ultrasonography (USG) of urinary tract and diethylene triamine pentaacetic acid (DTPA) and dimercaptosuccinic acid (DMSA) renal scans. Renal function was assessed by urine protein, levels of blood urea and creatinine, and glomerular filtration rate (GFR). VUR was graded according to the International Classification(4). All patients were started on low-dose antibiotic prophylaxis. Follow-up included 3-monthly urine cultures and yearly blood creatinine, urine protein and blood pressure measurement. DMSA scan was

initially done 6 months after the first scan and then yearly to assess renal scarring. DTPA scan was performed yearly to assess differential function of kidneys and GFR(5). Status of VUR and renal growth were monitored with yearly direct isotope cystourethrography (DRCG) and USG. In children with perceptible reduction of reflux on DRCG, a MCUG was also done for the purpose of grading. Renal growth was assessed by calculation of renal parenchymal volume(6) and by comparison of kidney length with bipolar parenchymal thickness. All episodes of febrile and culture positive urinary tract infection (UTI) were recorded. Age at presentation, grade of reflux, renal function tests, renal scars, time for resolution of reflux and necessity for surgical intervention were studied. The indications for surgery were single functioning kidney and recurrent breakthrough UTI (more than 2 UTI during 6 months) while on prophylaxis in children with grade IV-V reflux. The children who were operated continued to be followed up; weight and height were recorded at regular intervals.

Statistical analysis

Children were placed into 3 groups; group 1: complete resolution of reflux, group 2: persistent/improving reflux, and group 3: operated. Height and weight standard

deviation (z) scores were calculated at the time of entry into the study (HZ 1, WZ 1) and at last follow-up (HZ 2, WZ 2) using data from US National Center for Health Statistics, 1977 as the standard (Table I). Paired 't' test was used to compare HZ 1 with HZ 2, and WZ 1 with WZ 2 within each group. Unpaired 't' test was used to compare height and weight changes between the various groups; $p \leq 0.05$ was considered significant. Probability of persistence of reflux was studied by life table analysis (Fig.1).

Results

Thirty children (23 boys and 7 girls) were studied over 1-7 yrs with a total of 45 refluxing units. Two children had solitary kidneys. Two patients were seen on day 1 of life following antenatal diagnosis of hydronephrosis. The rest of the patients presented with UTI between 2 months - 12 yrs age (median 2 yrs). The age at inclusion in the study ranged from 1 day-12 yrs (median 3 yrs 3 months). Clinical features at the time of diagnosis included fever (25 subjects), loin pain (13), pyuria (4) and hypertension (4). Two patients, one with left grade III reflux and another with bilateral grade IV reflux had blood level of creatinine at 1.4 and 1.8 mg/dL respectively.

Complete resolution with medical management was seen in 3 units with grade V reflux over a period of 5 yr, 2 with grade IV

TABLE I: Comparison of z scores at entry and last followup(mean \pm SD)

Groups	Refluxing units	HZ 1	HZ 2	WZ 1	WZ 2
Complete resolution	IV-V: 5	-0.813 \pm 1.37*	0.783 \pm 1.22*	-0.78 \pm 1.06	-0.177 \pm 1.23
	I-III: 12				
Persistent reflux	IV-V: 22	-1.302 \pm 1.62	-1.594 \pm 1.41	-1.336 \pm 1.23	-1.54 \pm 1.06
Operated	IV: 6	0.226 \pm 1.38	0.128 \pm 0.89	-1.013 \pm 1.18	-0.446 \pm 0.8

HZ 1,WZ 1: Height and weight z scores at entry; HZ 2,WZ 2: Height and weight z scores at last follow-up

* P < 0.001

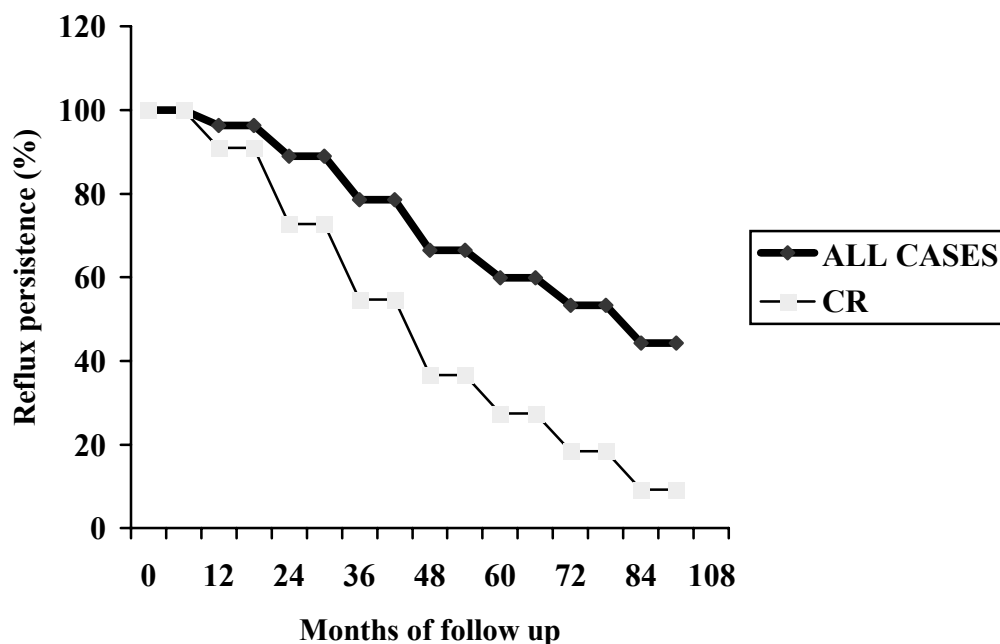


Fig. 1. Life table analysis showing probability of persistence of VUR among all cases and in the completely resolved (CR) group.

reflux over 2-3 yr and in all 12 units with grade I-III reflux over 6 months-6 yrs. Ureteric reimplantation was performed in 4 patients with grade IV reflux (6 units); 2 with bilateral pyonephrosis and 2 with single functioning kidney. One child with grade V reflux underwent pyeloplasty for associated pelvi-ureteric junction obstruction. Another with grade III reflux underwent nephroureterectomy of the nonfunctioning, opposite kidney to control hypertension (240/150 mm Hg).

Breakthrough UTI were seen in 12 patients, of whom 3 were surgically managed. In the medically managed group, 2 patients with grade IV-V reflux had recurrent infections. In one, this stopped following resolution of reflux along with improvement in growth parameters. In the other, surgery was not planned since reflux was seen to be regressing. In the operated group, two developed UTI in the first

year after surgery with no effect on growth parameters.

The refluxing and nonrefluxing sides showed focal defects on DMSA scan in 62.2% and 14.3% respectively; global reduction (20-40% of relative uptake) in 11% and 0% and shrunken kidney (relative uptake <20%) in 15.5% and 14.2% respectively, the majority occurring in grade IV-V reflux. Out of 13 children with bilateral grade IV-V reflux, significantly reduced function on one side was seen in 4 cases. No new scars or deterioration in renal function on renal scans developed during the period of study. Measurement of renal parenchymal volume at entry and last followup showed growth parameters within $\pm 2SD$ of normal values in 90% of the patients. GFR was maintained in all patients.

The mean height gain in group 1 was highly significant ($P \leq 0.001$). There was no

significant difference between HZ 1 and HZ 2, and WZ 1 and WZ 2 in the remaining groups. Statistically significant improvement in height ($P \leq 0.001$) and weight ($P \leq 0.05$) was seen in group 1 compared to group 2, and improvement in height in group 1 compared to group 3 ($P \leq 0.011$) (Fig. 2). Comparison between group 2 and 3 showed significant improvement in weight in favour of group 3 ($P < 0.05$).

'z' scores below -2 SD for height and weight were seen in 3 patients in group 2 (Table I); all had history of breakthrough UTI. Two patients had raised blood pressure of 120-160/110 mm Hg and multiple scars with one kidney smaller and poorly functioning with low GFR on DTPA scan; blood urea and creatinine levels were within normal limits.

The third patient had a blood pressure of 140/90, 24hr urine protein 1.2 g and blood creatinine of 1.8 mg/dL; USG showed bilateral small kidneys. USG showed significantly less parenchymal thickness in these children compared to the remaining in their group at the time of entry as well as last followup ($P \leq 0.05$).

Discussion

Primary VUR often improves with age(7,8). In our study, 15% of grade IV-V and all the cases of grade I-III reflux resolved completely over 6 months to 6 yrs. The statistically expected time of disappearance of reflux (Fig. 1) is in conformity with previous studies(9). In contrast to most international series(9), our series had a male-female ratio of 3:1.

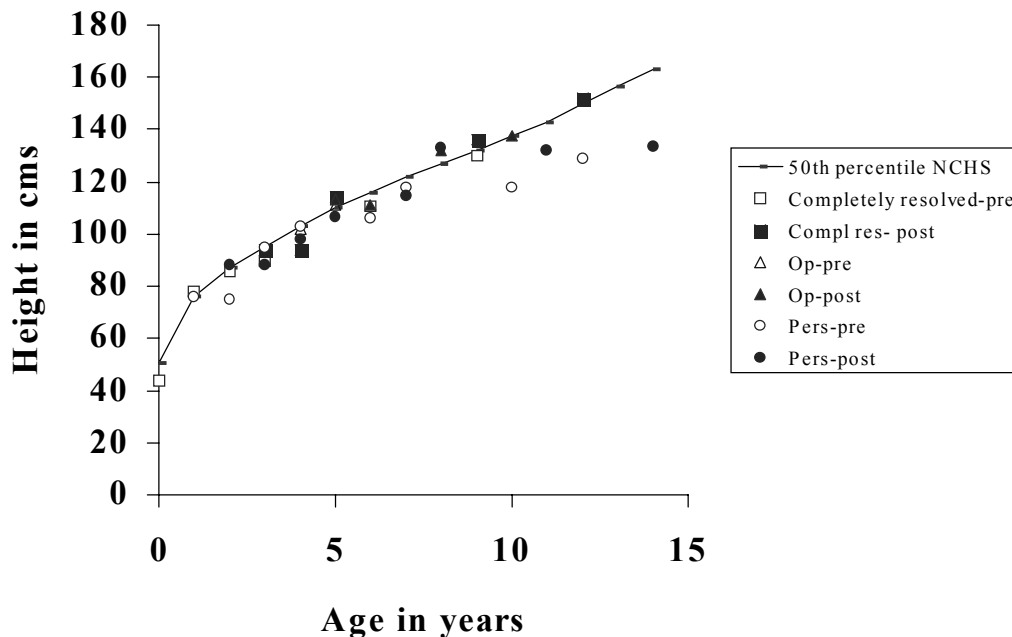


Fig.2 Scatter graph showing the 3 groups of patients with average heights at entry/time of operation and last follow-up plotted against the age in years with reference to the 50th percentile curve (NCHS standard). Each group is depicted by a separate symbol.

Key Messages

- Susceptibility to urinary tract infection continues even after successful surgery.
- Children with multiple renal scars, hypertension and poor renal functional volume show persistent growth retardation inspite of compliance with treatment protocols.

Our study has shown a higher incidence of initial renal damage compared to previous studies(10,11). Most of our patients were not on urophylaxis before entering the study with previous episodes of symptomatic bacteriuria. Pre-existing congenital abnormalities can also produce renal defects and may account for the damage seen on the contralateral nonrefluxing units(10,12). In spite of persistent severe reflux, no patient showed new scar formation or deterioration in renal function, probably because of constant medical supervision(13).

Although recurrent breakthrough infection is one of the most common indications for surgical intervention(14), UTI *per se* is independent of VUR, 2 of our 4 operated cases having UTI within a year of reimplantation(15). Socioeconomic status, breakthrough UTI and renal function play a role in somatic growth. The Hawthorne effect, *i.e.*, “a distortion of results caused by the response of the subjects to the special attention they receive from the researchers” should be kept in mind while interpreting data. No difference in growth was found in the first controlled trial comparing surgery vs conservative management in children below 11 yrs(2). Growth is not influenced by UTI or renal scars at entry (2,17,18). In our study, statistically significant improvement in height and weight was noted in the completely resolved group compared to the persistent refluxers, as noted by others(18). It remains to be seen whether the overall poor growth is also

in some way affecting the maturation of the vesicoureteral junction, delaying resolution of reflux. Better weight gain was seen in the operated children compared to those with persistent reflux. This is significant as this group was already biased towards poorer outcome.

In severe reflux, while surgical intervention is preferable with single functioning kidney, recurrent breakthrough infections and where regular follow-up appears unlikely, when the reflux is improving or the kidney is badly scarred, it is unlikely to be of much benefit. Renal scarring with associated hypertension, overall less functioning renal tissue and poor renal growth appear to have contributed to persistent growth retardation in three children with continuing reflux. The aim should therefore be to detect VUR early and maintain constant vigilance to prevent acquired renal scarring.

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