Renal scarring and vesicoureteric reflux

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SUMMARY A review of 105 children with urinary tract infection showed an increasing prevalence of grades II-III vesicoureteric reflux with diminishing age. During infancy reflux was almost always severe, and affected boys as often as girls. Radiologically scarred kidneys were drained by refluxing ureters in 98 % of cases. The prevalence of scars also rose significantly with increasingly severe reflux. Deterioration of existing scars or new scar formation was seen in 15 children; 18 out of 20 affected kidneys (90 %) were associated with grade III vesicoureteric reflux. 2 out of 5 children who developed new scars did so after 5 years of age.

Because severe reflux may occasionally be seen in the presence of a normal intravenous urogram, and since the finding of grades II-III vesicoureteric reflux is an indication for chemoprophylaxis, we consider cystourethrography essential in children of all ages with recurrent urinary tract infection. In children under 5 years the increased prevalence of both severe reflux and renal scarring are arguments for regarding cystourethrography as a necessary initial investigation.

Although bacteriuria and vesicoureteric reflux (VUR) are both common in childhood, their relative roles in the aetiology of renal scarring remain to be determined. Similarly the comparative value of long-term prophylactic chemotherapy and antireflux surgery in the management of VUR has not been clearly defined. As a preliminary to designing a controlled trial comparing surgery with conservative management of severe VUR, we carried out a retrospective study of children diagnosed as having urinary tract infection (UTI) and currently attending the Renal Clinic at Birmingham Children's Hospital. Our findings confirm statistically the observations of other workers (MacGregor and Freeman, 1975; Smellie *et al.*, 1975) that there is a striking relationship between the incidence of renal scarring and the severity of VUR, and also throw further light on the reputedly rare appearance of new renal scars in patients while under observation.

Patients and methods

The case records and radiographs of all children who attended the renal clinic during 1974 with recently diagnosed or previous UTI have been reviewed. Children with neurological disorders affecting bladder function, e.g. spina bifida, were excluded, as were those with anatomical urinary tract malforma-

tions, including all duplex anomalies, leaving 105 patients for the present analysis.

All patients were followed up for periods of up to 12 years, midstream urine specimens being examined microscopically at clinic attendance and cultured when indicated, as described by Robins *et al.* (1975). While in most cases the diagnosis of UTI was based on the finding of $\geq 10^5$ /ml pathogenic micro-organisms on culture of two fresh midstream urine specimens, or growth from urine aspirated suprapubically, a small number of earlier cases had been diagnosed on less stringent criteria.

All excretory urogram (IVU) examinations were reviewed; in each case the renal length was measured and the presence of renal scars, pelvicalyceal and ureteric dilatation and striations (Astley, 1971) were noted. We defined a radiologically demonstrable renal scar as loss of parenchymal thickness associated with distortion ('clubbing') of one or more underlying calyces, with or without irregularity of the renal outline. Thus, mere distension of calyces, with preservation of acute fornical angles and no loss of parenchymal thickness, was not considered to indicate a scar. Deterioration of an existing scar was defined as further parenchymal thinning with or without increased distortion of the underlying calyces, or extension of the scar to previously normal kidney tissue. Cystourethrogram (CUG) films were also reviewed and the severity of VUR graded as shown in Table 1. No instance of intrarenal reflux (Rolleston *et al.*, 1974) was seen.

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Table 1 Severity grading of vesicoureteric reflux (VUR)

Grade	Radiological features
I	Reflux on filling or micturition, into the ureter only
II	Reflux on filling or micturition, up to the pelvicalyceal system, but without distension
III	Reflux on filling or micturition, up to the pelvicalyceal system, and distending it

Table 2 Grade of VUR related to age at diagnosis, and the sex of 105 children with UTI

Grade of VUR	No. of children	Age at diagnosis and sex					
		< 1 yr		1-5 yr		≥ 6 yr	
		M	F	M	F	M	F
III	32	5	3	4	9	1	10
II	8		1	1	3	1	2
I	15			1	7	2	5
None	33			3	6	2	22
No CUG	17			3	6		8
All VUR	55	5	4	6	19	4	17
Total	105	5	4	12	31	6	47

Results

In Table 2 the incidence of VUR and its severity are related to the age when it was diagnosed and the sex of the 105 children. Each child is classified according to the maximal VUR shown in either ureter on any occasion. Although there were more than twice as many girls as boys with VUR, the female preponderance was not apparent during infancy. Moreover, the proportion of children exhibiting grades II-III VUR increased with diminishing age, the majority of infants being severely affected.

In Table 3 the incidence of scarring in 210 kidneys is related to the maximal grade of VUR shown in the ureters draining them. Since on theoretical grounds grades II-III VUR are more likely to be causally related to renal scarring than grade I VUR or none, we analysed grades II-III statistically as a single group,

Table 3 Grade of VUR related to incidence of renal scarring in 210 kidneys

Grade of VUR	No. of kidneys*	
	Total	Scarred (%)
III	47	37 (79)
II	13	5 (38)
I	30	6 (20)
None:		
unilaterally	20	0 (0)
bilaterally	66	1 (1.5)
No CUG	34	0 (0)

*Significance tests

None v I v (II + III): $\chi^2(v=2) = 84.45$; $P < 0.001$

(None + I) v (II + III): $\chi^2(v=1) = 77.39$; $P < 0.001$

II v III: $\chi^2(v=1) = 6.06$; $P < 0.025$

and this yielded the highest χ^2 values, though there was also a significant difference between grades II and III. Thus, although scars were seen with all grades of VUR, and in one instance where this was absent, the prevalence of scars rose significantly with increasingly severe VUR.

Details of 15 patients in whom existing scars deteriorated or new ones formed during follow-up are shown in Table 4. In Cases 7-10, who included 2

Table 4 Renal scar deterioration and new scar formation during follow-up

Case no.	Sex	Age at diagnosis (yr)	Age at deterioration (yr)	Grade of VUR	Recurrence of bacteriuria
<i>Scars initially present which deteriorated</i>					
1	F	7.0	9.3	III	Confirmed
2	F	9.0	11.2	III	No
3	F	3.2	4.3	III	Confirmed
4	M	2.1	5.9	III	No
5	M	7.2	10.3	III	No
6	F	5.1	7.5	I	Confirmed
<i>Possible scars which later became definite</i>					
7	F	3.5	4.5	III	No
8*	M	0.1	1.9	III	"
9	F	3.2	5.1	III	"
10*	M	0.1	1.5	III	"
<i>New scars observed at subsequent IVU</i>					
11	F	5.4	9.2	II	Confirmed
12*	F	4.1	6.5	III	No
13*	F	3.6	7.8	III	Probable
14*	F	2.6	5.9	III	No
15	F	7.5	9.2	III	Confirmed

*Bilateral scarring and VUR.

infants with 'gassy' abdomens at the time of IVU examination, we could not be certain whether scars were present initially, and these are shown as a separate group. In all 15 patients this deterioration had occurred by the time of the next IVU, and in 18 out of the 20 affected kidneys (90%) the draining ureter exhibited grade III VUR. UTI had been diagnosed in all the children at the time of presentation but, since most were subsequently maintained on chemoprophylaxis, only 5 had further episodes of confirmed bacteriuria before the radiologically observed deterioration.

Case reports

The case histories of 5 children (Cases 11-15, Table 4) in whom scars developed in eight previously unscarred kidneys are given, since this phenomenon is reputedly a rare occurrence (Blank, 1973; Smellie and Normand, 1975).

Case 11. A girl aged 5 years presented with left loin pain and fever. Diagnosis of UTI was confirmed and initial IVU (Fig. 1) was normal. 6 months later a

CUG showed grade II VUR on the left side. Clinic attendance was irregular and she had four recurrences of UTI during the next 3 years. Repeat IVU at age 9 showed marked parenchymal thinning at the left upper pole and clubbing of the underlying calyces (Fig. 2), while CUG showed persistent grade II VUR on the left side. The right side remained normal throughout.

Case 12. A 4-year-old girl was found to have UTI when investigated for 2 years' history of anorexia and lethargy. IVU showed normal appearances, but her

CUG showed bilateral grade III VUR. After initial treatment she received continuous chemotherapy, without demonstrable recurrence of UTI. 2 years later focal scarring with associated calyceal dilatation was seen at both upper poles. Although 7 years later there had been no further scarring, renal growth remained poor and bilateral grade III VUR persisted.

Case 13. A 7-year-old girl was referred in chronic renal failure and found to have shrunken kidneys. CUG (Fig. 3) showed bilateral grade III VUR, with

(a)

Fig. 1 Case 11. IVU, 1971. (a) Full-length, (b) cross-kidneys, (c) tracing of (b). Regular renal outlines, without scarring. Note the splenic impression on the left kidney. The pelvicalyceal systems are normal and the ureters undilated.

(b)

(c)

Fig. 2 Case 11. IVU, 1975. (a) Radiograph and (b) tracing. Marked parenchymal loss at the left upper pole, with clubbing of the underlying calyces. Normal right side.

Fig. 3 Case 13. CUG, 1974. Bilateral grade III VUR on filling, shown here, and increasing on micturition. Although the ureters are grossly dilated and tortuous and the bladder of large capacity, the latter emptied completely on voiding.

grossly dilated, tortuous ureters, suggesting that the reflux was longstanding. Normal ureteric peristalsis was observed on screening. Despite the large capacity of the bladder, it emptied completely and there was no evidence of neurological or obstructive lesions.

4 years previously an IVU carried out because of recurrent UTI was reported normal; review of the films showed no abnormality (Fig. 4). At that time CUG was not performed. Renal function continued to deteriorate and she received a cadaveric transplant 2 years later.

Case 14. Investigations for failure to thrive showed UTI in a 2-year-old girl. IVU showed slight generalised calyceal dilatation without scarring, and the CUG bilateral grade III VUR. Infection did not recur, but the next IVU, just before her sixth birthday, showed scarring at both upper poles, with marked calyceal clubbing and pelvic striation. 2 years later there was no further deterioration but bilateral grade III VUR had persisted and there was no renal growth.

Case 15. A 7-year-old girl was referred with a history of recurrent UTI treated by her general practitioner. Initial radiological examinations showed minimal dilatation of one of the right lower group of calyces without loss of renal parenchyma, and bilateral grade III VUR. Bacteriuria recurred 5 months later, but for the next 6 years she received continuous chemotherapy with no recurrence. Increased calyceal dilatation and lower pole scarring was present on the IVU carried out 20 months later. Subsequent radiological examinations showed no further scarring and satisfactory renal growth, while the VUR, although still bilateral, diminished in severity to grade I.

Discussion

Our findings agree with the well-established relationship between bacteriuria, reflux, and renal scarring (Smellie *et al.*, 1964, 1975). The correlation between VUR and scarring in our series is highly significant; 98% of damaged kidneys were drained by refluxing ureters. As others have reported (MacGregor and Freeman, 1975; McLachlan *et al.*, 1975; Smellie *et al.*, 1975), the prevalence of scarring rises with increasingly severe reflux. Moreover, 90% of kidneys in which new scars developed or existing ones deteriorated were associated with grade III VUR. Bailey (1973) introduced the term 'reflux nephropathy' for this association between VUR and renal scarring, removing the emphasis from infection as the primary cause of the scarring.

Although all the children whom we studied originally had infection and many experienced recurrences, it is noteworthy that only one-third of those showing scar formation or deterioration had demonstrable reinfection during the observation period. While this might be construed as indicating that VUR can cause renal damage in the absence of

(a)

(b)

Fig. 4 Case 13. IVU, 1970. (a) Radiograph and (b) tracing. Normal appearances, including undilated ureters.

bacteriuria, it must be appreciated that the radiologically apparent scar is a late manifestation of renal injury, and the finding of normal kidneys on IVU does not eliminate the possibility that the scarring process has already been initiated (Scott, 1975) as a result of previous infection associated with reflux. Although sterile reflux has been shown experimentally to cause renal damage in pigs (Hodson *et al.*, 1975), the mechanism was one of partial urethral obstruction, whereas in the children we have studied there was free bladder drainage. Moreover, in considerable experience of urological radiology in children without UTI (e.g. for recurrent haematuria, percutaneous renal biopsy, etc.), we have not seen the appearances characteristic of 'chronic atrophic pyelonephritis' (Hodson and Wilson, 1965). We therefore favour the view that infection plays a part in the aetiology of human renal scarring.

In assessing the value of surgical reimplantation of the ureter, the natural history of VUR must be taken into account. MacGregor and Freeman (1975)

reported complete disappearance in 44% and improvement in a further 14%, while Smellie *et al.* (1975) reported cessation in as many as 80% after prolonged follow-up. This phenomenon might explain the occasional renal scarring with minimal or no reflux, usually seen in an older child—for example Case 6. The effect of continuing, severe reflux on such damaged kidneys has not yet been fully assessed. The fact that scars can occasionally develop in previously normal kidneys suggests that it may, under certain circumstances, be harmful. Until this is more fully understood, the exact role of surgery in the management of VUR must remain uncertain, but we are now conducting a controlled trial in which age-matched children with VUR are randomly allocated to surgical or conservative management.

Much recent published evidence has emphasised the greater vulnerability of the kidneys to the effects of severe VUR during infancy (Rolleston *et al.*, 1970, 1975) and early childhood (Rolleston *et al.*, 1974; MacGregor and Freeman, 1975; Smellie *et al.*, 1975), and our findings support this. Community screening programmes have been directed mainly at schoolgirls (Savage *et al.*, 1973; Asscher *et al.*, 1973; Edwards *et al.*, 1975), and only small numbers of preschool children have been investigated (Davies *et al.*, 1974; Boothman *et al.*, 1974; Kunin *et al.*, 1976). The study of Boothman *et al.* (1974) suggests that bacteriuria is

by no means rare in boys under 5 years, in contrast to older boys (Kunin *et al.*, 1962; Meadow *et al.*, 1969). Moreover, our findings, like those of MacGregor and Freeman (1975) and Smellie *et al.* (1975), show at least as many infant boys as girls with reflux severe enough to be potentially damaging. Future screening programmes should focus attention on preschool children of both sexes.

It is also apparent that fresh scars may rarely develop after the age of 5 years, as illustrated by Cases 11 and 14 and as reported by Filly *et al.* (1974), Hugosson *et al.* (1976), and Smellie *et al.* (1975). Furthermore, we have on several occasions observed normal urographic appearances in the presence of grades II-III VUR (Figs 1-4), as did McLachlan *et al.* (1975). These findings have led us to question the management advocated by Bailey (1973) and by MacGregor and Freeman (1975), who argued that CUG was not indicated in a child over 5 years of age with UTI and normal kidneys on IVU. In our present state of knowledge, the finding of grades II-III VUR must indicate continuous chemoprophylaxis coupled with prolonged follow-up to protect the renal parenchyma from the potential risk of bacterial invasion. Despite its unpleasantness, we therefore consider CUG essential, even when the IVU is normal, in children of all ages with recurrent infections. In the case of children under 5, our finding of a higher prevalence of severe reflux, together with the acknowledged vulnerability of young kidneys to its effects, is a strong argument for regarding CUG in this age group as a necessary *initial* investigation.

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