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New renal scars in children with severe VUR: a 10-year study of randomized treatment

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Abstract The International Reflux Study in Children was set up to compare prospectively the outcome of medical or surgical management of children with grade III or IV vesicoureteral reflux and a history of symptomatic urinary tract infection. Development of new radiological scars was the main end point. Of the 306 children randomized, 302 (153 medical, 149 surgical) were available for radiological follow-up at 5 years. New scars had developed in 19 medically and 21 surgically treated children.

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Among 223 patients (113 medical, 110 surgical) who continued follow-up with urography at 10 years, only 2 further new scars developed. Overall, 47 new scars were acquired in 42 patients (20 medical, 22 surgical), 25 of them in children with unscarred kidneys at entry (13 medical, 12 surgical). New scars occurred mostly in children under 5 years of age and were observed more frequently in children with grade IV than grade III reflux. We conclude that with careful management, only a small proportion of children with severe reflux developed new scars and rarely after the first 5-year follow up period, and that there was no difference between children treated medically or surgically.

Keywords Vesicoureteral reflux · Urinary tract infection · Renal scar · Urography · Treatment trial

Introduction

The International Reflux Study in Children (IRSC) was designed to determine whether medical or surgical treatment is more effective in protecting children with grade III or IV vesicoureteral reflux (VUR) from renal damage. The development of new renal scars was defined as a main end point. At 5 years, a similar number of patients developed new radiological scars on serial intravenous urography (IVU) in the two treatment groups of both the United States branch (132 children) [1] and the European branch (306 children) [2, 3] of the study.

After completing the 5-year study, five of the eight original European participating centers agreed to extend the follow-up with clinical observation and an additional IVU at 10 years. The radiological results are reported in the 302 children who entered the study and were followed for more than 6 months, and in 223 children (113 medical, 110 surgical) who were followed radiologically for 10 years.

Patients and methods

The entry characteristics, exclusion factors, and management of children who entered the European limb of the IRSC have been reported [2, 3]. The children were under 11 years of age with grade III or IV VUR [4], without outflow obstruction, with a history of symptomatic urinary tract infection (UTI), and with a glomerular filtration rate ≥ 70 ml/min per 1.73 m^2 .

The methods have been fully described previously [2, 3, 5]. Serial IVU was performed using a standardized technique [5]. All IVU was evaluated by at least three experts blinded as to treatment; serial IVU was examined in each child without the corresponding cystograms. The renal parenchymal thickness was measured in the upper and lower poles and lateral zone, and the parenchymal area by planimetry. The results were expressed as the standard deviation score derived from a nomogram relating the measurements to the height of L1-L3 [6].

A radiological renal scar was defined as a calyceal deformity together with thinning of the overlying parenchyma [7]. Renal scars were typed according to Smellie et al. [8]: A with one or two scars, B affecting more than two areas but with some normal parenchyma remaining, C generalized irregular parenchymal reduction and calyceal deformity, and D small end-stage kidney.

In 4 (2 medical, 2 surgical) of the 306 patients reported previously [2, 3], IVU was not performed after 6 months from entry. They are omitted from this report.

Parallel $^{99\text{m}}\text{Tc}$ -dimercaptosuccinic acid (DMSA) imaging studies were also carried out [9] and will be reported separately. This paper reports the radiological findings.

Clinical follow-up was continued up to 10 years in 252 children. The final outcome will be published separately. There was no difference in entry characteristics between the treatment groups among the 302 children who completed 5 years and the 223 who had an IVU at 10 years (Table 1) or the 29 patients with only a 10-year clinical follow-up (12 medical, 17 surgical). Among the 302 children, 155 (51%) had unscarred kidneys at entry and 147 had established scars, 102 (34%) unilateral and 45 (15%) bilateral, with similar proportions among the 223 followed for 10 years. The proportions of children with different severity of scarring were similar in those managed medically and surgically (Table 1).

Cohen and Politano-Leadbetter were the main surgical techniques used [10]. Low-dose antibacterial prophylaxis with nitrofurantoin or trimethoprim (alone or in combination with sulfonamide) was continued for 6 months after successful surgery, or in the medical group until VUR had resolved or improved to grade I. If kidneys were unscarred, prophylaxis was usually discontinued at the age of 8 years. Regular complete voiding, double micturition at bedtime, and regular bowel action were also recommended. At 5 years, VUR with dilatation was seen in 57 (56%) of 102 children managed on a medical regimen, but at 10 years this was reduced to 27 (26%) [11].

Statistical methods

The computer software used for analysis was SAS for PC, version 8 (SAS Institute, Cary, N.C., USA). Statistical methods have been described previously [5, 10]. The outcome was analyzed according to 'intention to treat'. A life-table analysis and generalized rank test of Gehan-Wilcoxon was performed to compare both groups in the primary outcome of exponential distributed events of renal scars. Because of successfully completed stratified randomization, it was not necessary to take any co-variable into account.

The study protocol was approved in accordance with the standards in the declaration of Helsinki by the local ethics committee of each participating hospital and by the External Monitoring Committee of the Study.

Results

During the first 5-year period, 40 children developed new radiological scars, 19 medical (23 kidneys) and 21 surgical (22 kidneys) (1 patient was reported late) [2, 3]. Of these children, 28 were among the 223 followed radiologically for 10 years (14 medical, 14 surgical).

Between 5 and 10 years' follow-up, only 2 new scars developed among 223 patients, both in girls (1 medical, 1 surgical):

- A girl entered aged 3.8 years with left grade IV VUR and unscarred kidneys, managed medically. At 5 years, her IVU remained normal, VUR had improved, and was absent at 10 years. No further UTI was recorded during follow-up, but her 10-year IVU at 14 years of age showed a type A scar in the left upper pole. The DMSA study showed a new image defect.
- A girl entered aged 4.3 years with a history of recurrent UTI, bilateral VUR, right grade II, left grade IV, and bilateral renal scarring types A and B. Left ureteral reimplantation was successful. A febrile UTI occurred 18 months later, but thereafter no further UTI was reported. IVU was unchanged at 5 years, there was no VUR at 10 years, but the final IVU (aged 17 years) showed a further single left renal scar developing in a normal area of the scarred kidney. No new image defect was seen on the DMSA scintigraphy, but there was a reduction in the proportionate function from 33% to 28%.

Table 1 Renal status and maximum reflux grade at entry in each treatment group of 302 children (229 girls, 73 boys) followed for up to 5 years and of 223 children (166 girls, 57 boys) followed for 10 years (VUR vesicoureteral reflux)

Renal status	Patients followed up to 5 years			Patients followed up to 10 years		
	Medical	Surgical	Total	Medical	Surgical	Total
No scarring	75	80	155	57	53	110
Scarred	78	69	147	56	57	113
Unilateral	52	50	102	37	42	79
Bilateral	26	19	45	19	15	34
Total	153	149	302	113	110	223
VUR severity						
Maximum grade III	30	24	54	16	20	36
Maximum grade IV	123	125	248	94	93	187
Total	153	149	302	110	113	223



Fig. 1 Life-table analysis (Kaplan-Meier curves) showing the time of detection of new renal scars in children treated medically (*broken line*) and surgically (*unbroken line*). The difference was not significant ($P=0.57$, log-rank test)

Of 155 children who had unscarred kidneys at entry, 25 (16%) (12 medical, 13 surgical) developed new scars. In 17 children (8 medical, 9 surgical), scars developed in new areas of previously scarred kidneys (12% of 147). The type of the new scars is shown in Table 2. Of the 47 new scars, 25 (53%) were of type A. The type C scars in the surgical group were all left-sided and related to postoperative obstruction in 5 of the 7 children. One medically treated boy developed bilateral type C scars. In 8 of the 25 children who developed new radiological scars in kidneys that were normal on IVU at entry, the DMSA image at entry was already abnormal. New scars were observed more frequently in children with grade IV reflux, 38 of 248 (15%), compared with grade III reflux, 4 of 54 (7%, $P<0.05$).

Table 3 indicates the age at entry of children developing new scars in each treatment group, and the age at which the new scars were detected. More new scars developed among children under 5 years of age (in 31 of 42 children), with similar numbers in each treatment

Table 2 Type of new scar acquired over 10 years in 47 kidneys (42 patients)

New scar type	Medical	Surgical
A	14	11
B	7	5
C	2	7
D	1	–
Total	24	23

Table 3 Age in years at last intravenous urography (IVU) without a new scar and at first IVU with new scar according to treatment group

	Age without new scar (years)	Total	Age at first IVU with new scar (years)			
			<2	2 to <5	5 to <11	≥11
Medical <i>n</i> =20	<2	9	6	3		
	2 to <5	8		6	2	
	5 to <11	3			2	1
Surgical <i>n</i> =22	<2	9	7	2		
	2 to <5	9		7	2	
	5 to <11	4			1	3
Total		42	13	18	7	4

group. New scars were observed in 14 boys, 12 of them <2 years of age at entry, and in 28 girls, 11 of them <2 years of age at entry.

The timing of the observation of new scars is demonstrated on the Kaplan-Meier curves (Fig. 1). New scars were detected sooner after entry among surgically than medically treated patients, but this difference was not significant ($P=0.57$, log-rank test).

Discussion

In this multicenter study comparing medical and surgical management of a large number of children with grade III or IV VUR and a history of symptomatic UTI, there was no difference after 5 years in the numbers of patients acquiring new radiological scars between the two treatment groups among 306 patients randomized [2, 3]. This has been the experience of others conducting similar studies over 5 years [1, 12, 13]. However, in few other studies has careful observation continued for 10 years [14]. In the large international trial reported here, only 2 further patients acquired new scars between 5 and 10 years of follow-up, 1 in each treatment group, 1 in a previously normal kidney and 1 in a kidney with already established scarring.

Although not statistically significant, new scars tended to be observed earlier in the surgical than in the medical group. Seven surgical patients, including 3 boys under 2 years of age, developed type C scars compared with 1 medically treated child. However, in both treatment groups most new scars developed under the age of 5 years.

Recent studies on familial reflux have indicated the genetic factors that may predispose to VUR [15]. Permanent renal damage may be present at birth, particularly in infant boys, and is usually associated with severe VUR [16]. This needs to be differentiated from acquired damage that is seen more often in girls who are more prone to recurrent UTI [17, 18, 19]. However, it has not usually been possible on DMSA studies to differentiate between congenital and acquired damage without serial investigations, since it is difficult to distinguish between acute uptake defects caused by inflammation and established permanent damage. In the study reported here, based on good-quality serial IVU, it has been possible to identify change from structurally normal unscarred kid-

neys to scarred kidneys. These changes have been seen in similar proportions in the two treatment groups over a period of 10 years. New scars were observed especially in the younger children, and it should be noted that such scars were also found in 14 boys, 12 of whom were <2 years of age at entry. It is of interest that 8 patients who entered the study with unscarred kidneys on IVU but abnormal DMSA images subsequently showed a new radiological scar at the corresponding site.

Some variations in renal morphology and areas of thinned parenchyma were observed during serial prospective radiological follow up. These have been documented and discussed [2]. However, the IRSC study was carried out according to a protocol aimed at determining the outcome of two methods of treatment based on the development of well-defined new scars, but was not designed to examine the pathogenesis of such scarring. At the end of 10 years there was no difference between the treatment groups in the acquisition of new scars.

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