

*Original article*

## Reflux nephropathy in the 1st year of life – the role of infection

Marie Sheridan, Fiona Jewkes, and David C. S. Gough

Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA, UK

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**Abstract.** The importance of infection and vesico-ureteric reflux in the development of reflux nephropathy is generally accepted. Widespread use of antenatal ultrasound scanning has identified dilated fetal urinary tracts, allowing prompt investigation and treatment in the early post-natal period; some of these children have vesico-ureteric reflux. This study compares renal parenchymal damage, demonstrated by uptake of technetium  $^{99m}$  dimercaptosuccinic acid (DMSA) in two groups. The first included babies less than 6 months old who had presented with their first urinary tract infection and had vesico-ureteric reflux. The second included those in whom a dilated urinary tract had been identified at antenatal ultrasound and post-natal investigation revealed vesico-ureteric reflux, but who had no evidence of urinary tract infection. Renal damage was present in 68% of group 1 and 29% of group 2 when DMSA scanning was used to detect scarring ( $P = <0.05$ ). Our results support the proposal that infection is a major factor in development of renal damage in patients with vesico-ureteric reflux. Identification by antenatal ultrasound scanning allows early therapeutic intervention before renal damage occurs.

**Key words:** Antenatal hydronephrosis – Vesico-ureteric reflux – Urinary tract infection – Reflux nephropathy

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### Introduction

The occurrence of vesico-ureteric reflux and infection was first recognised in 1903 [11]; it was almost 60 years later that Hodson and Edwards demonstrated the association between vesico-ureteric reflux and renal scarring [5]. The importance of the combination of urinary tract infection and vesico-ureteric reflux in the pathogenesis of renal scarring and dysfunction – so-called reflux nephropathy – has

now been widely recognised [10, 14]. This observation has provided the incentive to detect vesico-ureteric reflux early so that urinary tract infections may be avoided in these patients, either by administration of prophylactic antibiotics or, in appropriate cases, by surgery.

Since the advent of antenatal ultrasound scanning, increasing numbers of babies with dilated urinary tracts have been identified in utero, and investigation in the first few weeks of life has shown that a proportion of these are due to vesico-ureteric reflux [1, 13]. In 1987, Scott reported pelvicalyceal system dilatations in seven babies detected on antenatal ultrasound that were found to be due to vesico-ureteric reflux on investigation in the neonatal period [12]. Of these seven cases, impaired renal function was demonstrated by radioisotope studies in four, none of whom had detectable evidence of urinary tract infection, lending weight to the theory that vesico-ureteric reflux and renal dysfunction may both be part of a developmental abnormality of the renal tract [7] and casting doubt on the efforts of medical or surgical treatment to influence the ultimate outcome of upper tract change in patients with reflux.

This study attempts to compare the extent of renal dysfunction, using radioisotope studies, in babies with vesico-ureteric reflux and urinary tract infection and babies who presented antenatally with reflux before infection occurred.

### Materials and methods

We reviewed our clinical and radiological experience of 36 patients who had presented to the Royal Manchester Children's Hospital within the last 6 years. In the first group were 17 babies who presented to hospital within the first 6 months of life with urinary tract infection as confirmed by suprapubic aspiration of urine or serial clean-catch specimens. Ultrasound examination and contrast micturating cystourethrography (MCUG) had been performed within 14 days of documented urinary tract infection. Relative renal function was assessed by renal uptake of technetium  $^{99m}$  dimercaptosuccinic acid (DMSA) during the acute stage, and also between 3 and 6 months following the infection. The later scan was used for comparison, to avoid inclusion of isotope uptake abnormalities occurring temporarily in the acute stage of infection. In the second group were 19 babies in whom dilated renal tracts had been identified during antenatal scanning. Within the first 48 h of life all babies had ultrasound

**Table 1.** Sex distribution and age at presentation in groups 1 (clinical urinary tract infection) and 2 (antenatal hydronephrosis)

Presentation	Group 1 Infection	Group 2 No infection
Age (mean)	14 weeks	7 weeks
Sex	6 girls 11 boys	3 girls 16 boys

**Table 2.** Split renal function (dimercaptosuccinic acid uptake) in refluxing patients

Group 1 Infection		Relative %	Group 2 No infection	
%	Number		%	Number
29	5	50:50	68	13
29	5	60:40	5	1
23	4	70:30	0	0
19	3	80:20	11	2
0	0	90:10	16	3
100	17		100	19

examinations to confirm renal tract dilatation. Contrast MCUG and DMSA scans were not performed acutely, but all babies awaiting investigation were treated with chemoprophylaxis in the form of trimethoprim 2 mg/kg per day. In none of these cases did the baby develop a urinary tract infection (Table 1).

## Results

All babies had vesico-ureteric reflux demonstrated on MCUG, with all patients refluxing into dilated systems (grades III, IV, and V according to international scale).

In the group presenting with urinary tract infection the mean age at diagnosis was 14 weeks (range 1 to 25 weeks, group 1). In those presenting antenatally, the mean age at the time of investigation was 7 weeks (range 5 days to 15 weeks, group 2). In all cases where nephropathy was present on DMSA scan there was associated vesico-ureteric reflux.

For the purposes of tabulation and analysis, the DMSA percentage was rounded up where the figure was 5% [e.g. split DMSA 55/45 was rounded to 50/50. Split DMSA 72/28 was rounded to 70/30.

The results in Table 2 show that normal split function was present in 29% of babies in group 1, compared to 68% in group 2. Uneven split renal function was found in 71% of babies in group 1 and 32% in group 2 ( $P < 0.05$ ). The  $\chi^2$ -square test was used to compare normal and abnormal split renal function in the two groups.

## Discussion

Ransley and Risdon [8] put forward the "big bang" theory of reflux nephropathy, which suggested that with vesico-ureteric reflux of significant grade and intrarenal reflux the initial urinary tract infection results in a local inflammatory

response in those segments where intrarenal reflux occurs, causing renal parenchymal damage and ultimately scar formation. The results from our study support the theory that infection plays a major role in renal damage.

In those patients with vesico-ureteric reflux and urinary tract infection, 71% showed evidence of renal parenchymal damage as demonstrated by impaired uptake of DMSA. In the group in which vesico-ureteric reflux alone was present, only 32% showed evidence of renal damage. This does, however, leave a significant minority of patients in whom there was evidence of renal parenchymal damage in the absence of infected urine, and raises the question of the effects of reflux of sterile urine on the renal parenchyma.

It has been suggested that the pressure effects of vesico-ureteric reflux and intrarenal reflux alone can cause some degree of renal damage in the absence of infection. Hodson et al. succeeded in producing scarring in refluxing kidneys of pigs with sterile urine [6]. The model used, however, was essentially one of bladder outflow obstruction and their results were not reproduced by other workers [9]. More recently Godley et al. [4] failed to demonstrate that vesico-ureteric reflux alone had any significant effect on renal uptake of DMSA even in the presence of high voiding pressures and abnormal detrusor function.

Mackie and Stephens [7] have proposed the theory that both vesico-ureteric reflux and renal dysplasia are part of the same developmental abnormality of the ureteric bud. This can explain the recognised association between the small dysplastic kidney and vesico-ureteric reflux occurring in infancy; the reduced renal uptake of DMSA in 32% of patients diagnosed antenatally in our study supports this theory.

The high proportion of male patients in both groups is noteworthy. Reflux is more common in females [3], however, in a review of reflux in boys, Decter et al. [2] reported that 25% of their patients presented at ages less than 3 months. Of the seven cases presented by Scott, six were in males [12]. These results suggest that in the neonatal period reflux may be more common in males than in females.

In the first 6 months of life infection is a major factor in the development of renal parenchymal damage in patients with vesico ureteric reflux, and antenatal ultrasound scanning may provide one avenue of therapeutic endeavour that identifies patients before renal damage occurs.

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