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Original article

Long-term prognosis of post-infectious renal scarring in relation to radiological findings in childhood – a 27-year follow-up

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Abstract. In a previous report the long-term prognosis of 30 patients with renal scarring after pyelonephritis in childhood was described. In this study, we have related the extent of renal scarring present in childhood to the conditions in early adulthood. A radiological progression of scarring from childhood to adulthood was seen in one-third of the kidneys. The 7 patients with bilateral scarring in childhood had a smaller renal area, lower glomerular filtration rate and higher plasma vasopressin at follow-up than 13 healthy controls. The 20 patients who had unilateral scarring in childhood had a smaller renal area, lower glomerular filtration rate, higher diastolic blood pressure and higher plasma renin at follow-up than controls; 4 had hypertension. The most important finding was that children with unilateral disease are at risk of serious long-term complications. Filtration fraction at follow-up was higher in patients with extensive renal scarring in childhood compared with those with a normal renal area or small scars in childhood ($r = -0.43$, $P < 0.05$). This may indicate glomerular hyperfiltration by remnant glomeruli. This paper emphasizes the potential seriousness of childhood urinary tract infections especially when early infantile infections are overlooked. A follow-up of more than 4 decades may be necessary before the ultimate prognosis can be established, especially in patients with unilateral renal disease. It is advised that most patients with post-infectious renal scars are followed as high-risk patients, and that treatment continuity is established between paediatricians, nephrologists and, when required, obstetricians.

Key words: Reflux nephropathy – Urinary tract infections – Pyelonephritis – Radiological appearance – Renal function – Hypertension – Follow-up

Introduction

We have earlier reported on the clinical course, blood pressure control and regulating hormones, and renal function in 30 patients 27 years after a scar was first detected [1]. Here we describe details of the radiological appearance at first IV urogram (IVU) in childhood and relate this to the outcome of the disease. The study was undertaken to examine whether or not the long-term prognosis could be predicted from the radiological appearances in early childhood. We were especially interested in evaluating the prognosis of unilateral renal lesions. Such studies might contribute to a more individualized managment during adolescence and the childbearing years in order to better prevent or mitigate renal functional deterioration.

Patients and methods

We reviewed all reports of IVUs performed at the Department of Paediatric Radiology at the Karolinska Hospital between 1951 and 1967. Children with a history of febrile urinary tract infections and with at least unilateral focal renal scarring on IVU were selected for study, as previously described [1]. Children with signs of obstructive renal malformations or compromising diseases, e.g. diabetes mellitus, were excluded. Post-infectious renal scarring (reflux nephropathy) was defined as signs of calyceal clubbing with a corresponding reduction of the renal parenchyma directly overlying clubbed calices [2]. Through the Swedish Central Bureau of Statistics we were able to trace 47 of the 53 patients who fulfilled our criteria for eligibility. Thirty of these patients (26 women, 4 men) agreed to take part in the follow-up examinations (Table 1). The mean age at first IVU was 6 years (range 9 months to 13 years) and at follow-up 33 years (22–41 years). The mean follow-up was 27 ± 6 years. This group of patients has recently been described in detail [1].

Table 1. Age and sex of patients and controls

	At presentation $n = 30$	At follow-up $n = 27$	Controls $n = 13$
Sex (female/male)	26/4	24/3	10/3
Mean age and range (years)	6(0.75–13)	33(22–41)	34(25–41)

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Table 2. Classification of renal scarring according to Smellie et al. [3]

Type A	Mild; not more than two scarred areas
Type B	Severe; more generalized, but some areas of normal tissue persist
Type C	Irregular thinning of renal tissue, superimposed on a generalized calyceal deformity
Type D	End-stage shrunken kidney with little or no function

At follow-up, 3 patients (10%) had developed end-stage renal disease (ESRD). The remaining 27 patients, of whom 6 had undergone unilateral and 1 partial nephrectomy, underwent a thorough examination of renal function, blood pressure regulation and some regulating hormones. Twenty-one of these patients, of whom 6 had been unilaterally nephrectomized, agreed to a follow-up IVU, but 6 patients did not. All drugs were withdrawn 7 days before the kidney function tests. The same studies, including IVU, were performed in 13 healthy volunteers, 10 women and 3 men, mean age 34 years (range 25–41 years). All controls had normal kidneys on IVU and no history of symptomatic urinary tract infection.

Renal function and blood pressure regulation tests. Glomerular filtration rate (inulin clearance), renal plasma flow (para-aminohippuric acid clearance), renal blood flow, filtration fraction, fractional clearances of sodium, potassium and phosphate, the urinary albumin excretion, serum and urine β_2-microglobulin, plasma renin activity, angiotensin II, vasopressin, aldosterone, systolic and diastolic blood pressures and mean arterial blood pressure were determined as previously described [1]. All records were made by the same nurse. All patients and controls gave informed consent and the study of both patients and healthy controls was approved by the Ethics Committee of the Karolinska Hospital.

Radiological examination. IUVs in both childhood and adulthood were analysed with regard to whether the renal damage was uni- or bilateral. The renal parenchymal loss in individual kidneys was classified according to Smellie et al. [3], Table 2. Voiding cysto-urethrography had been performed in 26 children. Only part of these radiographs had been saved. According to the original report from 1951–1967, vesico-ureteric reflux to the renal pelvis was present in 21 of these children (81%). Five children (19%) had no or only minor reflux not reaching the pelvic region. In this paper we report only whether the reflux reached the pelvis and whether it was dilated or not in childhood. No cysto-urethrography was performed in adults.

Follow-up IVU was performed in connection with the renal function tests. The patients received an IV injection of contrast medium (60% Urografin, Schering AG, Berlin, Germany) in a dose of 0.5–0.75 ml/kg body weight. A film focus distance of 100 cm was invariably employed. Radiograms obtained at 5 min after the IV injection of contrast medium were considered particularly suitable for assessment. Utilizing the same films the outlines of each collecting system and kidney were planimetrically established. The area of the collecting system was then subtracted from the total renal area and the results correlated to the body surface area (BSA) [4] and/or to the length of the lumbar segment L1–3 [5]. Progression of renal scarring was defined as either development of scars in previously healthy kidneys or as development of new scarred areas in kidneys with scars present already in childhood (for instance type A to type B or type B to type C).

Statistical analysis. Results are given as mean ± standard deviation. Analysis of variance, Students' *t*-test and Mann-Whitney U-test were used for paired and unpaired observations. Correlation coefficients were calculated by Pearson's method. The chi-squared test with continuity correction was used.

Table 3. Radiological findings at first IV urogram (IVU) in childhood and at follow-up

	At first examination	At follow-up
	$n = 30$	$n = 21$[a]
Renal scarring		
Unilateral[b]	20(67%)	8(53%)
Bilateral	10(33%)	7(47%)
Unilateral nephrectomy		6[c]
Mean total renal parenchymal area (SD)[d]	−3.4 ± 2.5	−2.3 ± 3.9
VUR reaching the pelvis	21/26[e]	NE

VUR, Vesico-uteric reflux; NE, not examined

[a] Six patients did not agree to follow-up IVU and 3 had end-stage renal disease (ESRD)

[b] In 6 patients with unilateral scarring in childhood, bilateral scars could be seen at follow-up

[c] Six patients had undergone unilateral nephrectomy, among these 3 of the remaining kidneys had developed type A scarring, 1 a type B scarring and 2 were still normal

[d] Compared with healthy children and adults respectively. Patients with ESRD or unilateral nephrectomy at follow-up were excluded

[e] According to the original report. Only part of these radiographs had been saved

Table 4. Progression of renal scarring in individual kidneys from childhood (60 kidneys) to adulthood (48 kidneys)[a]

	Childhood *n*	Follow-up *n*	*n*
Normal	20	16	10 Normal
			5 Type A
			1 Type B
Type A	3	2	2 Type A
Type B	12	10	6 Type B
			2 Type C
			2 ESRD
Type C	22	17	3 Nephrectomized
			9 Type C
			1 Type D
			4 ESRD
Type D	3	3	3 Nephrectomized

[a] Including 6 kidneys of 3 patients who had developed ESRD at follow-up. Six patients did not agree to follow-up IVU

Results

Radiological examinations in childhood and at follow-up

Some of the radiological findings are summarized in Tables 3, 4, and 5, others are given below. At follow-up 3 patients had developed ESRD at ages 17 (male), 31 and 34 years (females). Their childhood IVUs were classified as B/B, C/C and C/C, respectively. Six patients had undergone unilateral nephrectomy (3 of these kidneys were classified as type C in childhood and 3 as type D).

At follow-up, the mean total renal area – the 6 nephrectomized patients excluded – was reduced compared with healthy controls (99 ± 12 cm^2 BSA for the patients vs 127 ± 12 cm^2 BSA for the healthy controls ($P < 0.001$)].

Table 5. Results of renal function, blood pressure and blood pressure regulating hormones at follow-up in 30 patients with reflux nephropathy and 13 healthy controls in relation to extent of renal scarring in childhood

	Childhood urograms		
	Unilateral scarring $n = 20$	Bilateral scarring[a] $n = 10$	Controls $n = 13$
Renal area in childhood (SD)	–2.7	–4.8****	NE
Renal area at follow-up (SD)[b]	–0.6	–5.6***,****	0.5
Renal area at follow-up (cm^2)[b]	101***	90***	127
GFR (ml/min per 1.73 m^2)	90**	87*	108
RPF (ml/min per 1.73 m^2)	489**	414***	587
RBF (ml/min per 1.73 m^2)	787**	686***	989
FF(%)	19	20	19
SBP (mm Hg)	127	117	116
MAP (mm Hg)	98**	93*	86
DBP (mm Hg)	84**	81*	72
PRA (ng/ml per hour)	1.6*	1.0	0.9
A II (pmol/l)	25	44	21
Aldo (pmol/l)	297	290	229
AVP (pmol/l)	2.5	3.7*	2.0
U-Alb (mg/l)	11	7*	4
U-β2 (mg/l)	0.6	0.4	0.4
s-β2 (mg/l)	1.6**	2.1***,****	1.3

* P <0.05 vs healthy controls; ** P <0.01 vs healthy controls; *** P <0.001 vs healthy controls; **** P <0.05 bilateral vs unilateral reflux nephropathy. All other comparisons between the two groups NS
GFR, Glomerular filtration rate; RPF, renal plasma flow; RBF, renal blood flow; FF, filtration fraction; SBP, systolic blood pressure; MAP, mean arterial blood pressure; DBP, diastolic blood pressure; PRA, plasma renin activity; A II, angiotensin II; Aldo, aldosterone; AVP, vasopressin; U-Alb, urinary albumin excretion; U-β_2, urine β_2-microglobulin; s-β2, serum β_2-microglobulin
[a] Patients with ESRD were not examined at follow-up
[b] Patients who had undergone nephrectomy were excluded

Table 6. Renal function, blood pressure and PRA at follow-up in 20 patients with unilateral reflux nephropathy in childhood in relation to extent of renal damage in the scarred kidney

	Extent of scarring in damaged kidney			
	A or B[a] $n = 5$	C[b] $n = 12$	D[c] $n = 3$	P*
GFR (ml/min per 1.73 m^2)	93±12	89±19	90±12	NS
RPF (ml/min per 1.73 m^2)	510±109	482±110	481±26	NS
FF (%)	19±2	19±4	19±3	NS
DBP (mm Hg)	86±14	84±12	80±13	NS
PRA (ng/ml per hour)	2.3±1.1	1.3±0.9	1.1±0.5	NS

* Analysis of variance
[a] Four patients had type B scarring and 1 type A in childhood. Of these, 1 patient who had a normal kidney and contralateral type A scarring in childhood had bilateral type A scarring at follow-up; 2 patients who had unilateral type B scarring in childhood had unilateral type C at follow-up while 2 were unchanged from childhood
[b] Three type C kidneys had been removed during follow-up. One type C kidney had developed type D scarring and 1 normal kidney had developed type B scarring during follow-up. In the remaining 7 kidneys the status was unchanged
[c] All 3 type D kidneys had been removed during follow-up of the contralateral kidneys, 2 remained normal in adulthood, while 1 developed a type A lesion

The renal area in childhood correlated significantly with the renal area at follow-up IVU (total area $r = 0.62$, P <0.02; right kidney $r = 0.83$, P <0.001; left kidney $r = 0.80$, P <0.001). Neither those with unilateral, nor those with bilateral damage showed full compensatory hypertrophy (Table 5).

Table 4 shows the progress of scarring in individual kidneys from childhood to adulthood. We surmized that the 6 ESRD kidneys were of type D. A progression of renal scarring was seen in 15 of 42 non-nephrectomized kidneys, i.e. 36% (Table 4). In 6 of 16 (38%) kidneys judged as normal in childhood, renal scarring was visible at follow-up.

Morphological examinations of nephrectomized kidneys

Reports from histological examinations were available for 5 of 6 removed kidneys. Focal renal scars were observed in all, in some described as wedge shaped. Chronic inflammation with sclerosed glomeruli, atrophic tubules and fibrosis were described in all. The scars had a fairly distinct demarcation from healthy tissue. It was pointed out that there were no cartilage, primitive ducts or ductules, or other structures suggesting congenital dysplasia. Calices underlying cortical scars were in some instances described as dilated.

Renal function and blood pressure control in relation to the extent of renal scarring in childhood

Results of renal function, blood pressure and regulating hormones in relation to the presence of unilateral or bilateral renal damage in childhood and the Smellie classification of the IVUs in childhood [3] are presented in Tables 5 and 6. As seen in Table 5, patients with unilateral and bilateral renal scarring differed from healthy subjects in several respects. Renal function was generally better in patients with unilateral disease compared with those with bilateral damage, but the differences did not reach statistical significance (Table 5).

Patients with unilateral scarring had significantly lower fractional potassium excretion (21%) compared with controls (27%, P <0.05), but there were no differences in fractional sodium or phosphate excretion between patients with unilateral or bilateral disease compared with controls (data not shown). When values for adult renal function, blood pressure and plasma renin of 20 patients with unilateral renal disease in childhood were related to the extent of renal damage in the scarred kidney in childhood, no significant differences were found (Table 6).

Complicatons in relation to extent of scarring in childhood

All the 3 patients who developed ESRD had bilateral scarring in childhood (Table 7). Of the 7 patients who had

Table 7. Complications of childhood reflux nephropathy in 30 patients in relation to extent of renal scarring in childhood

	Unilateral scarring	Bilateral scarring
ESRD ($n=3$)	0	3
Hypertension (>140/90 mm Hg) ($n=7$)	4	3[a]
Toxaemia of pregnancy ($n=2$)	0	2
GFR at follow-up <65 ml/min per 1.73 m^2 ($n=2$)	1	1

[a] All 3 with ESRD

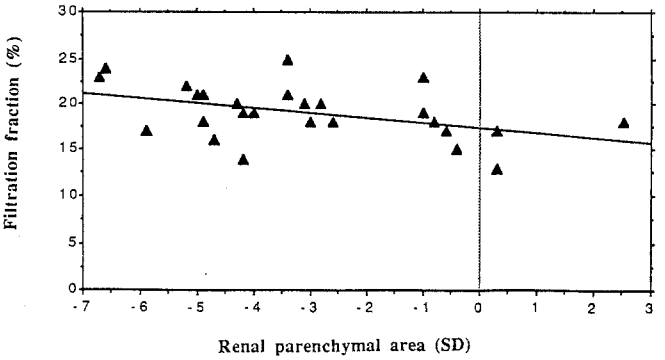

Fig. 1. Filtration fraction in adulthood in relation to renal parenchymal area in childhood ($r = -0.43$, $P < 0.05$)

hypertension at follow-up (>140/90 mm Hg), 3 (all with ESRD) had bilateral and 4 had unilateral disease in childhood (Table 7). Of the latter 4, 1 had unilateral type A damage as a child and bilateral type A at follow-up, 1 had unilateral type C damage as a child and the same at follow-up, 2 had unilateral type C or D scarring as children and had undergone nephrectomy at follow-up. In both, the spared kidney was normal on follow-up IVU.

Two patients had a glomerular filtration rate of less than 65 ml/min per 1.73 m^2 at follow-up. The one with a glomerular filtration rate of 61 ml/min per 1.73 m^2 had bilateral scarring in childhood and normal blood pressure at follow-up, while the patient with a glomerular filtration rate of 55 ml/min per 1.73 m^2 had unilateral scarring in childhood and hypertension at follow-up (Table 7).

Renal haemodynamics in relation to renal parenchymal area

To investigate whether glomerular hyperfiltration was present the renal haemodynamics in the adult patients was related to the renal parenchymal area. The renal area as measured by childhood and adult urograms correlated positively with renal plasma flow ($r = 0.41$, $P < 0.05$ and $r = 0.54$, $P < 0.02$, respectively) and inversely with filtration fraction ($r = -0.43$, $P < 0.05$, Fig. 1 and $r = -0.50$, $P < 0.03$, respectively), but did not correlate with glomerular filtration rate.

Progression of renal scarring in relation to infections

In the 24 patients in whom progression of parenchymal damage could be evaluated (21 patients who had a follow-up IVU and 3 with ESRD), 10 of 12 patients with progress in one or both kidneys during follow-up had recurrent symptomatic urinary tract infections compared with 5 of 12 without progress (data not shown). This difference was not statistically significant ($P = 0.09$).

Discussion

We reported recently on the long-term follow-up of the present group of 30 patients [1]. In summary, 3 (10%) had developed ESRD, 7 (23%) had hypertension and 2 women (13%) developed severe toxaemia of pregnancy. In the 27 patients without ESRD, glomerular filtration rate and renal plasma flow were significantly lower than in healthy controls, while diastolic blood pressure was higher. In the present paper we have analysed relations between the extent of the renal damage in childhood and the outcome in adulthood.

The children with the most extensive renal damage ran the greatest risk of developing ESRD before the age of 30–40 years. The main finding in the present paper is that unilateral scarring, as judged from IVU in childhood, may be associated with serious consequences such as a persistently lowered glomerular filtration rate and renal plasma flow, an increase in plasma renin activity and hypertension. For example, in 3 of the 4 non-ESRD patients with hypertension, the scarring was still unilateral in adulthood, and in 1 patient with unilateral scarring in childhood the glomerular filtration rate was so low (Table 6) that she probably is at risk of developing ESRD in the future. Longer follow-up than 3 decades may be necessary before the prognosis can be adequately evaluated, especially in patients with so-called unilateral renal damage.

The prognosis of the patients in the present study was worse than we had expected. The mean age at the first recorded attack of pyelonephritis was 4 ± 2.8 years. Since most onset infections occur during the 1st year of life, the high mean age indicates a diagnostic and therapeutic delay, which next to obstruction seems to be the strongest predictor of renal damage [6]. The findings emphasize the potential seriousness of childhood infections especially when early infantile attacks of pyelonephritis are overlooked.

The lowered total renal area and renal function in patients with unilateral renal lesions show that the presumed unaffected kidney in several instances was unable to react with a compensatory hypertrophy, which suggests that both kidneys were in fact damaged. This is not surprising since acute pyelonephritis in early childhood is most often bilateral [7]. It has recently been shown that renal *Escherichia coli* infections can inhibit cell division as mea-

sured by the DNA content of renal tissue [8]. Such a mechanism may interfere with the growth potential of the kidney following acute pyelonephritis, even if no obvious scars are seen. With the use of CT scans and ^{99m} technetium dimercaptasuccinic acid scintigraphy one might better identify otherwise overlooked lesions than with IVU and improve the evaluation of the prognosis [9, 10].

Surprisingly, in patients with unilateral scarring in childhood there was no relation between renal function and blood pressure at follow-up and the grade of scarring in the damaged kidney (Table 5). Presumably the healthy rather than the focally scarred kidney determined the prognosis. Our findings support previous observations [11–13] that the renin-angiotensin system is involved in the pathogenesis of the hypertension, but the mechanisms are still enigmatic. Unfortunately we did not investigate the genetic predisposition for essential hypertension.

The pathogenesis of the deterioration in renal function in this group of patients is still under debate. The patients with the smallest total renal parenchymal area both in childhood and adulthood had a higher filtration fraction than patients with more limited damage. In previous studies of glomerular changes and function in pyelonephritis, both opposition to and support of the hyperfiltration theory have been reported [14, 15]. Our finding that the glomerular filtration rate decreases relatively less than renal plasma flow, resulting in an increased filtration fraction, seems consistent with the finding of glomerular hypertrophy and increased vessel wall thickness in patients with reflux nephropathy [14], and are thus in favour of the hyperfiltration hypothesis. Wikstad et al. [16] studied adult patients who either were born with one single kidney or had been unilaterally nephrectomized during the first years of life. A progressive deterioration of renal function in the remaining, originally healthy kidneys, was demonstrable, but not until the age of 30–40 years. Their findings are very similar to ours and show that deterioration can occur even in the absence of infection.

An experimental study suggests that systemic as well as intraglomerular hypertension in association with hyperfiltration are the main factors causing progressive structural and functional renal damage [17]. Our study also suggests that adaptive haemodynamic changes, such as elevation of mean arterial blood pressure [1], occur before the lowering of the glomerular filtration rate and might have contributed to the deterioration in renal function seen in these patients. Early detection of hypertension is probably of paramount importance in postponing renal functional deterioration. In our group of patients we tried to provoke hypertension by physical exercise but without success [18]. We found, however, a considerable increase in vasopressin release in some patients, the physiological importance of which is unknown.

There was no clear-cut evidence that the number of recurrent infections during adolescence and adulthood was directly related to the outcome in adult life. Our patient numbers are, however, too limited to evaluate this issue. A factor complicating this question is that patients with pyelonephritic renal scarring have an increased accessibility of receptors on uro-epithelial cells for pyelonephritogenic *E. coli* [19] and may therefore be more susceptible to renal damage.

Significant albuminuria which correlates with the presence of focal and segmental glomerulosclerosis [20] has been shown to be an important predictor of progressive renal failure in reflux nephropathy [14, 20, 21]. This is not invariably true since patients with severe unilateral renal scarring may have significant albuminuria only from the scarred and not from the healthy kidney. In the present study, albuminuria was significantly higher in patients with bilateral disease compared with controls, but some patients with unilateral disease had increased albuminuria which probably originated from the damaged kidney.

We advise that most patients with post-infectious renal scars are followed as high-risk patients, and that treatment continuity is established between paediatricians, nephrologists and, when required, obstetricians.

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Ask the expert*

What is the value of measuring urinary citrate in the management of a child with renal tubular acidosis?

Key words: Citrate – Renal tubular acidosis

Measurement of citraturia is a convenient but not an obligatory step in the management of a child with distal renal tubular acidosis (RTA). Monitoring of blood gases and urinary calcium excretion is generally sufficient for this purpose. Measurement of citraturia has no value in the management of a child with proximal RTA. Hypocitraturia is present in distal, but not in proximal RTA. The reduced citrate excretion observed in distal RTA is probably due to the combined effects of decreased luminal pH in the proximal tubule, intracellular acidosis and potassium depletion [1]. The increase in urinary citrate observed in proximal RTA may be due to inhibition of proximal citrate reabsorption caused by the elevation of both luminal [2] and intracellular pH [3].

Citrate is a chelator of calcium and an inhibitor of calcium phosphate and oxalate crystallization [4]. Treatment of distal RTA should aim, therefore, not only to correct the systemic acidosis but also to normalize calcium and citrate excretion. Unfortunately, the amount of alkali needed to correct the acidosis is often not enough to raise citrate excretion to the normal range [5]. This is more easily accomplished in infants and young children than in patients with established nephrocalcinosis. It is possible that moderate degrees of renal insufficiency contribute to the persistence of hypocitraturia [6]. The citraturic response of patients with stones to potassium citrate is greater than after identical doses of potassium bicarbonate [7]. This is also our experience in the treatment of children with distal RTA and, for this reason, sodium and potassium citrate therapy is preferred. Although the major effect of citrate on urinary citrate excretion is attributable to its metabolism to alkali, an additional effect could be due to excretion into the urine of intact, non-metabolized citrate.

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* The editors invite questions for this section