Retrospective study of children with renal scarring associated with reflux and urinary infection

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Abstract

Objective—To review the histories of children with bilateral renal scarring and severe vesicoureteric reflux to determine whether an improvement in early management might reduce the risk of scarring.

Design—Retrospective study of medical records and discussion with parents.

Setting—Outpatient departments of two teaching hospitals.

Patients—52 children aged 1-12 years participating in a randomised comparison of medical and surgical management. All had a history of symptomatic urinary tract infection. Two thirds presented with fever and two with hypertension or renal failure. In only one out of 32 children examined by antenatal ultrasonography was an abnormality suspected.

Results—There was delay in diagnosis or appropriate imaging or effective treatment of urinary infection in 50 of the 52 children. In 41 there was delay in diagnosis; there was delay in treating a confirmed infection in 45; no antibacterial prophylaxis was prescribed before imaging in 28; and investigation of the urinary tract was delayed in 33. The severity of scarring was significantly related to delay in diagnosis (χ^2 for trend 7.43, $P=0.01$). Four children of mothers known to have reflux nephropathy were not investigated until they developed urinary tract infection.

Conclusions—Efforts to reduce the incidence and severity of renal scarring should be directed towards rapid diagnosis and effective early management of urinary tract infection in infancy and childhood. Siblings and offspring of known patients with severe reflux nephropathy should be investigated for reflux.

Introduction

Renal scarring found in association with vesicoureteric reflux (reflux nephropathy) is an important cause of hypertension and end stage renal disease in children and young adults and is to some extent preventable. Although damage associated with severe reflux can be developmental and may occur in utero,¹ there is abundant clinical and experimental evidence that renal scarring can be acquired at any stage in childhood and that urinary infection as well as vesicoureteric reflux is important in its pathogenesis.²⁻⁹ Factors of particular importance in the acquisition of scars include the growing kidney of a young child, delayed treatment of urinary infection, recurrent urinary infection, and the more severe grades of reflux.³⁻⁵ It has been shown experimentally that when reflux and infection are present the rapid introduction of antibacterial treatment can arrest or prevent the development of scarring.¹⁰⁻¹²

Urinary tract infection has a prevalence of 1-2% in girls and less than 1% in boys. Vesicoureteric reflux has been found in 35-40% of children with urinary infection. Renal scarring has been found in a third of those with reflux, in 12% of all infected children, and in a quarter of those with a history of recurrent urinary infection.¹³

To study factors in the development of renal scarring

in children, we reviewed retrospectively the early histories and management of a group of 52 children seen at the two hospitals because of bilateral severe reflux, established bilateral renal scarring, and a history of urinary tract infection to ascertain whether their renal damage might have been limited or prevented.

Patients and methods

Twenty four boys and 28 girls aged 1-14 years were studied. They were born during 1974-88 and were participating in a randomised prospective controlled trial personally supervised by one of us (JMS) of medical versus surgical management of their reflux. Four children had controlled hypertension, and the glomerular filtration rates estimated by clearance of ethylene diaminetetra-acetic acid labelled with chromium-51 ranged from 24 to 124 ml/min/1.73 m² (median 75), four of them being below 30 ml/min/1.73 m². Those with obstruction of outflow from the bladder and other structural abnormalities of the urinary tract were excluded. Reflux extended up to the kidney in all renal units. Renal scarring was diagnosed under the age of 2 years in 13 boys and eight girls and between 2 and 9 years in 11 boys and 20 girls.

All the children had a history of urinary infection, with symptoms not always related to the urinary tract. The early history of urinary infection was therefore the main focus of the study. Details of presentation, treatment, and patient's and family history were obtained from clinical records and from referring hospitals and family doctors (NPP and AP). Further specific information was obtained by a structured interview with the parents (AP).

CRITERIA FOR CLASSIFICATION

Delay in diagnosis of urinary tract infection was recorded if no urine sample was cultured when there was a period of acute symptoms related to the urinary tract or high fever lasting for at least five days¹⁴; when there were ill defined symptoms (such as abdominal pain or screaming attacks) for at least one month; when there were one or more previous episodes with symptoms similar to those present when urinary tract infection was first diagnosed; or when there was delayed bladder control, defined as any daytime wetting at age 5 years or over or night time wetting at 7 years or over.

Delayed or inadequate treatment was recorded when the diagnosis had been delayed (when inevitably treatment was also delayed); more than four days had elapsed after collection of urine before the start of effective treatment¹⁴; or low dose antibacterial prophylaxis had not been prescribed either between treatment of the presenting infection and investigation or after the diagnosis of reflux.

Delayed or inadequate investigation was recorded when cystography was excluded from the initial investigation; cystography was delayed for more than one month in a child not receiving prophylaxis; adequate imaging of the kidneys was omitted from the initial investigation; investigation was not performed until after infection had recurred¹⁵; or a family history

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of vesicoureteric reflux or reflux nephropathy was disregarded.

These criteria were based on standard practices, recommendations,¹⁴⁻¹⁶ and experience.^{5,8}

Renal scarring was diagnosed by intravenous urography according to the standard criteria and classified radiologically as previously described.^{2,17} In type A there were one or two scars only; type B more than two scarred areas; type C generalised parenchymal thinning with deformity of all papillae; and type D a small, poorly functioning, end stage kidney. Table I shows the types of scarring in pairs of kidneys in relation to sex. Type A scarring was more common in girls than boys, and seven boys and three girls had type C scarring. Impaired uptake of dimercaptosuccinic acid labelled with technetium-99m was also shown in all affected kidneys.

Results

There was delay in one or more of the above criteria in 50 of the 52 children in this study. The median date of onset of symptoms was 1983, and in 35 the diagnosis of urinary infection was made between 1983 and 1988.

DIAGNOSIS OF URINARY TRACT INFECTION

Diagnosis was delayed in 41 of the 52 children, 21 boys and 20 girls (table II). The longest recorded delay was four years and 11 months. All 13 patients in whom symptoms started in the first six weeks of life had a delay in diagnosis ranging from seven days to two years. Symptoms in infancy were mainly non-specific, whereas in older children they were more often related to the urinary tract. Fever was the presenting symptom in 34; in two the symptoms were due to hypertension or renal failure. In three children with longstanding bed wetting, urinary infection was first diagnosed by the school doctor at ages 5, 7, and 9 years, when investigation showed bilateral renal scarring. No delay in diagnosis was recorded in 11 children, three boys and eight girls.

TREATMENT OF URINARY TRACT INFECTION

Appropriate treatment, including the prescription of prophylaxis, was delayed in 49 children. In 45 of them effective treatment of the presenting infection was delayed (table II). In 41 this was secondary to delay in diagnosis. In five of these 41 and two whose condition was diagnosed immediately there was evidence that treatment was not instituted for between six days and eight months. In two others the prescribed

antibiotic failed to clear the infection; one progressed to septicaemia, and the infection persisted for three weeks in the other. Thus treatment was delayed or ineffective in at least nine children known to have urinary infection at the time.

Prophylaxis—Low dose antibacterial prophylaxis was prescribed immediately after treatment of the acute infection in 15 children. In nine others it was started four to 12 months later, after one or more recurrences of infection and before investigation. In 28 children (in all of whom infection recurred) no prophylaxis was prescribed until after reflux had been diagnosed (more than a month later in 25 of them). Even after reflux had been identified there was further delay in prescribing prophylaxis of two to four months in three of them and more than one year in four others.

Recurrence of infection—In 31 children there was a clear history of recurrent symptoms or persistent day or night wetting before diagnosis. After confirmation of urinary infection, 37 of the 52 children had one or more further infections before starting prophylaxis.

INVESTIGATION

After the infection had been diagnosed imaging was delayed or inappropriate in 33 of the 52 cases reviewed.

Interval to diagnosis of vesicoureteric reflux—In 15 children, three without prophylaxis, reflux was identified within one month of diagnosis of the infection. In 37, 25 without prophylaxis (table II), cystography was performed two months to six years and seven months after diagnosis of the infection. Reflux was diagnosed in the first six weeks of life in four infants, by the age of 2 years in a further 21, between 2 and 5 years in 13, and aged 5 years or over in 14. In 26 children ultrasonography was the initial investigation. Either dilatation or hydronephrosis was noted in 12, but in 14 (five of whom with symptoms that had started in the first 6 weeks no ureteric dilatation or renal abnormality was reported).

Antenatal ultrasonography, family history, and new scar development—The single abnormal result of ultrasonography of the fetal renal tract found in the 32 mothers who underwent antenatal ultrasonography was reported as urinary tract dilatation only. Four mothers were known to have reflux nephropathy. Four of their five children had bilateral reflux and bilateral renal scarring when first investigated aged 6 weeks to 7 years, after urinary tract infection (the fifth, not included in this study and with no history of infection, had bilateral reflux and normal kidneys). Ten children were reported to have structurally normal kidneys on their initial intravenous urograms (confirmed retrospectively in eight of them). In five others only one kidney was scarred initially, though subsequently both kidneys were affected. In the 37 other children the first intravenous urogram already showed bilateral scarring.

Relation between scar type and delay in diagnosis of urinary infection—All the children included in the study had bilateral renal scarring (table III). Among the 11 children without any delay in diagnosis the types of scars seen were AA (two), AB (seven), AC (one), and BD (one). There was up to six months' delay in diagnosis in 24 children, 13 of whom had severe scar types (AD, BB,

TABLE 1—Numbers of children with bilateral reflux and renal scarring after urinary infection according to sex and type of scarring

Sex	Type of scarring in pairs of kidneys*							
	AA	AB	AC	AD	BB	BC	BD	CC
Girls	6	10	2	1	6	1	2	0
Boys	1	7	1	1	5	3	3	3
Total	7	17	3	2	11	4	5	3

*A—one or two scars; B—more than two scarred areas; C—generalised parenchymal thinning with deformity of all papillae; D—small, poorly functioning end stage kidney.

TABLE II—Details of delays in diagnosis and treatment of urinary infection in 52 children with bilateral renal scarring

Age at onset of symptoms	No of children	Delay in diagnosis of infection		Delay in effective treatment		Delay in diagnosis of reflux without prophylaxis	
		No of children	Delay	No of children	Delay	No of children	Delay
<6 Weeks	13	13	Seven days to two years	13	Three weeks to eight months	4	Two to seven months
6 Weeks <2 years	20	13	Seven days to four years and 11 months	13	Six days to six weeks	11	Two months to three years and seven months
2 Years <5 years	10	7	Three weeks to four years and five months	10	Three to four weeks	5	Two months to six years and seven months
≥5 Years	9	8	Three weeks to four years	9	Seven weeks	5	Two months to two years and five months
Total	52	41	Seven days to four years and 11 months	45	Six days to eight months	25	Two months to six years and seven months

TABLE III—Delay in diagnosis of urinary infection in children related to type of scarring*

Renal scarring	Delay in diagnosis of urinary infection (months)			Total
	0	≤ 6	> 6	
Moderate†	10	11	6	27
Severe‡	1	13	11	25
Total	11	24	17	52

* χ^2 for trend in mean scores = 7.43, df = 1, $P = 0.01$, Yates's correction.

†Scar types AA, AB, and AC, see methods.

‡Scar types AD, BB, BC, BD, and CC, see methods.

BC, BD, or CC). Among the 17 children in whom there was delay of more than six months 11 had more severe combinations of scar types. There was a significant relation in the type of renal scarring between no delay and delay of more than six months ($\chi^2 = 6.32$; $P = 0.01$, Yates's correction) and also a significant trend ($\chi^2 = 7.43$; df = 1; $P = 0.01$, Yates's correction; see table III).

Discussion

The renal scarring associated with vesicoureteric reflux is a serious condition but symptomless unless detected by investigation of one of its complications or of urinary infection. It was an unexpected finding in most of the children studied.

Examination of the possible antecedents of renal damage reported in this necessarily selected group of 52 children has identified areas for potential improvement in the management of all but two.

DETECTION AND TREATMENT OF REFLUX

The symptoms of urinary infection are well known to be diverse and often non-specific, particularly in infants and young children, in whom the growing kidney is most susceptible to infective damage and when incompetence of the vesicoureteric valve is more likely to be present. Failure to consider the diagnosis was clearly an important factor contributing to the delay in this series. An alternative clinical diagnosis such as a viral illness had sometimes been made, and, particularly in young children, urine collection was often not attempted. In some instances there was delay in consulting the doctor—for example, in families who moved house frequently or because of language difficulties, family illness, or stress. Only two thirds of the children presented with a febrile illness. Similar delays in diagnosis were also encountered by the South Bedfordshire General Practitioners Group¹⁸ and by Jadresic *et al.*¹⁹ In our series there was a significant relation between the delay interval from onset of symptoms to diagnosis of urinary infection and the severity of renal scarring.

The exact timing of the start of treatment was not

always easy to obtain retrospectively, but it seemed that microbiological confirmation after several days was usually awaited before treatment was started. (The use of nitrite sticks, urinoscopy, or microscopy would enable rapid preliminary diagnosis.¹⁴ The records conveyed little sense of urgency about the children's management, although the importance of delay in starting treatment as a factor in the acquisition of scars has been emphasised previously.^{3,5} For example, Winberg *et al* found that the incidence of scarring was four times greater in a group of girls with delayed treatment than in a comparable group treated immediately.³ There is also strong supportive evidence from animal studies.¹¹⁻¹³

The prescription of prophylactic antibacterial treatment after a urinary infection and until the cause has been identified has been recommended in the guidelines published by the Royal College of Physicians.¹⁴ This was done in only 15 of the 52 children. Even in the 29 in whom prophylactic treatment was delayed until after the diagnosis of reflux there was a further delay in its introduction in seven.

PREVENTION OF SCARRING

In a later study by the South Bedfordshire General Practice Group 11 out of 23 children with renal scarring in their practices received suboptimal management, in that investigation was delayed.²⁰ In our study the most important imaging delay was in the diagnosis of reflux; in 37 (71%) three quarters of them without prophylaxis, the delay was over two months and up to six and a half years. It was unfortunate that 14 of the 25 in whom initial ultrasonography was performed were incorrectly reassured because no abnormality of the renal tract was reported. The main purpose of investigating children with urinary infection is to identify those with renal abnormalities or at risk of developing them. Views suggesting that a cystogram may not be necessary or that ultrasonography is a sufficient examination to exclude renal scarring clearly need revision.

Ideally reflux should be recognised before infection occurs and a search in siblings and offspring of index patients with severe reflux or reflux nephropathy offers an opportunity to do this^{21,22}—an opportunity that was missed in the four families with known maternal reflux nephropathy in our study. The discovery of reflux or reflux nephropathy in the five children of these four mothers supports the findings of Bailey *et al*²¹ and Aggarwal and Verrier-Jones,²² and the strong recommendations of Bailey *et al* that infants born to parents with reflux nephropathy or severe reflux or who have affected siblings should be investigated as soon after birth as possible. At least 14 other children in our study had siblings with vesicoureteric reflux, details of whom will be reported separately.

Whether some or all of the scarring in the children in this study might have been prevented or limited can only be a matter for speculation in a retrospective study. Some of the children probably had abnormal kidneys at birth, but on the initial intravenous urogram of 13 children one or both kidneys were structurally normal, bilateral scarring developing subsequently. Surprisingly an abnormality of the fetal renal tract was reported in only one of the 32 mothers undergoing antenatal ultrasonography, repeated in some as late as 32 weeks' gestation. Vesicoureteric reflux in infancy, however, is not always preceded by dilatation of the fetal urinary tract detected on antenatal ultrasonography,²³ and Gordon *et al* have shown that renal scars can be acquired early in infancy after infection of a refluxing urinary tract.²⁴

CONCLUSION

If acquired renal scarring is to be limited or prevented

Clinical implications

- The renal scarring associated with vesicoureteric reflux and found in 10-20% of children with urinary infection is serious and can be followed by hypertension or renal failure
- Clinical and experimental studies have established that delay in treatment of urinary infection is a factor in the development of scarring
- Delay in diagnosis and treatment of urinary infection or identification of reflux was found in 50 out of 52 children with bilateral renal scarring and bilateral reflux studied retrospectively
- The severity of the scarring was significantly related to the length of delay in diagnosis of infection
- The possibility of urinary infection should be considered in any infant or child who is feverish or unwell

urinary tract infection must be suspected, diagnosed, and treated rapidly in infancy and childhood and further infection prevented during follow up. It is also essential to identify vesicoureteric reflux early by investigation with cystography in infants with antenatal dilatation of the urinary tract, infants and young children after a first urinary infection, and siblings and offspring of patients with renal scarring. These measures will reduce the risk in children of the later development of reflux nephropathy and its complications.

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Ten year mortality in patients with suspected acute myocardial infarction

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Abstract

Objective—To describe the 10 year mortality in patients with suspected acute myocardial infarction.

Design—Follow up of all patients below 76 years of age admitted with acute chest pain to 16 coronary care units participating in the Danish verapamil infarction trial in 1979-81.

Subjects—Of the 5993 patients included, 2586 had definite infarction, 402 had probable infarction, and 3005 did not have infarction.

Main outcome measures—Death and cause of death. Standardised mortality ratio (observed mortality/expected mortality in background population).

Results—The estimated 10 year mortalities were 58.8%, 55.5%, and 42.8% in patients with definite, probable, and no infarction, respectively ($P < 0.0001$). Stratified Cox's analysis identified a hazard ratio for mortality of 1.25 (95% confidence interval 1.08 to 1.44) for probable infarction compared with no infarction and of 1.15 (1.00 to 1.32) for definite compared with probable infarction. The standardised mortality ratio in the first year was 7.1 (6.5 to 7.8) for definite infarction, 5.0 (3.6 to 6.3) for probable infarction, and 4.7 (4.2 to 5.2) for no infarction. From the second year and onwards the annual standardised mortality ratio in the three groups did not differ significantly. Cardiac causes of deaths were recorded in 89%, 84%, and 71% of the deaths in patients with definite, probable, and no infarction, respectively.

Conclusions—The 10 year mortality of patients with and without infarction is significantly higher

than in the background population. Most deaths are caused by coronary heart disease, and these patients should consequently be further evaluated at the time of discharge and followed up closely.

Introduction

The short and long term mortalities in patients who have recovered from an acute myocardial infarction have previously been evaluated.¹⁻⁷ During the past decade increasing attention has been paid to patients admitted to coronary care units with suspected infarction but in whom the diagnosis is ruled out (no infarction). The short term prognosis has been the subject of several studies,⁸⁻¹² whereas long term studies are few, with observation periods up to five years and mainly retrospective.¹³⁻¹⁵ These studies indicated that the mortality in patients without infarction continues to be high for several years after discharge; in the first three years it is almost three times higher than that in the background population.¹⁶

We compared the 10 year mortality from day 15 after admission in patients with no infarction with the mortality in patients with infarction and with the expected mortality in the general population in Denmark.

Patients and methods

From 1 June 1979 to 15 August 1981, 6631 patients below 76 years of age were consecutively admitted with suspected myocardial infarction to one of 16 coronary