PAPERS AND SHORT REPORTS

Glomerular filtration rate in schoolgirls with covert bacteriuria

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Abstract

Clearance of technetium-99m-labelled diethylenetriaminepenta-acetic acid was used to measure total and individual kidney glomerular filtration rates in 48 girls with covert bacteriuria. The mean ($\pm$ SD) of the total rates of 18 girls with scarred kidneys (99 ± 24 ml/min/1.73 m²) was significantly ($0.005 > p > 0.002$) lower than that in 30 girls with unscarred kidneys (119 ± 18 ml/min/1.73 m²). This reduction in glomerular filtration was related to the loss of kidney substance associated with scarring rather than to vesicoureteric reflux. The glomerular filtration rate was unrelated to the duration of bacteriuria.

These findings suggest that in girls aged 4 and over neither vesicoureteric reflux nor covert bacteriuria contributes to the progression of kidney damage.

Introduction

Chronic pyelonephritis is an important cause of end-stage kidney failure in children,^{1,2} and its close association with vesicoureteric reflux has been observed repeatedly.³⁻⁸ Not surprisingly considerable time and effort has been expended on eradicating infection and correcting vesicoureteric reflux in an attempt to prevent the kidney damage associated with urinary tract infection. Most kidney scars develop before the age of 4 years.⁹ In prospective studies of schoolgirls over 4 scarring rarely develops in kidneys which are normal at the outset of the observation period even when vesicoureteric reflux is present

and infection is left untreated.^{10,11} This suggests that treatment may not be necessary in girls over 4 in whom the kidneys are radiologically normal.

Little is known about the effect of vesicoureteric reflux and urinary tract infection on renal function, and before a policy on non-treatment is advocated it seems prudent to evaluate the effect of these factors on the glomerular filtration rate. We report such a study.

Subjects and methods

Study population, follow-up, and treatment—In 1971, 89.3% of all 4-11-year-old schoolgirls (n=13 369) in the City of Cardiff were screened for bacteriuria by means of a mobile laboratory.¹² In 207 girls (1.7%) covert bacteriuria was identified. All bacteriuric girls were allocated at random to a treatment or control group. The treatment group received short (mostly seven-day) courses of antimicrobial agents whenever colony counts exceeded 10⁵ colony-forming units/l. Drug treatment was selected on the basis of "Multi-disk" sensitivity of the urinary isolates. During the initial four-year follow-up girls were seen four to six times a year, but subsequently they attended the clinic once or twice yearly or more often if indicated clinically.

Radiological investigations—When first seen during 1971 and 1972 excretion urography and micturating cystography were carried out on all 207 girls. These investigations were repeated in 1975-6 after a follow-up period of four years.¹³ In 1979, 120 of the 207 girls who were then aged 12-19 were still attending the clinic. Consent to measure glomerular filtration rate was obtained from 60, and in 48 the investigation was completed. Table I gives the original radiological findings in the 48 girls. Eighteen of the girls had scarred kidneys, and in two the scarring was bilateral. Vesicoureteric reflux had been detected in 25 girls, and there were 35 kidneys which were drained by refluxing ureters; in 11 of these the vesicoureteric reflux was associated with renal scarring. Reflux was graded 1-3, as described by the Medical Research Council Bacteriuria Committee.¹⁴ Where the two original investigations had shown differing severity of reflux the most severe grade was used for analysis.

Measurement of glomerular filtration rate—Girls were asked to have a normal fluid intake on the morning of the investigation and were given a 300 ml drink shortly before the study. They were then asked to lie supine on a couch which was positioned over the gamma camera so that both kidneys could be visualised. Technetium-labelled

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stannous diethylenetriaminepenta-acetic acid was administered by rapid intravenous injection. The dose was adjusted according to the weight of the subject. Each girl received 10 MBq (0.27 mCi) plus 1.5 MBq (0.04 mCi)/kg. The gamma-camera study started at the time of the injection and continued for 30 minutes. Blood samples were taken two, three, and four hours after injection for estimation of glomerular filtration rate.¹⁵ The percentage contribution from each kidney was assessed from the relative uptake over the first three minutes of the study.¹⁶ All values obtained were corrected for surface area and expressed per 1.73 m².

TABLE 1—Distribution of renal scarring and vesicoureteric reflux in 96 kidneys from 48 girls with covert bacteriuria (grade of reflux given in parentheses)

Radiological findings	Vesicoureteric reflux	No vesicoureteric reflux	Total
Scarred kidneys	11 { (1) 2 (2) 3 (3) 6 (1) 5 }	9	20*
Normal kidneys	24 { (2) 13 (3) 6 }	52	76
Total	35 { (1) 7 (2) 16 (3) 12 }	61	96

*Scarring bilateral in two girls.

Bacteriological methods—At each clinic visit a midstream urine specimen was collected after perineal washing with green soap solution and cultured on dipslides. Identification of organisms was carried out by standard techniques,¹⁷ and the sensitivity of the isolates to antimicrobials was determined by the disc-diffusion method. All subjects were sent dipslides at two-month intervals; of the 48 girls studied, 22 returned these slides regularly, 12 returned them occasionally, and 14 never returned them. Bacteriuria was regarded as significant if there was a pure growth of $>10^8$ colony-forming units/l urine. If the specimen showed a mixed growth a further dipslide was sent and significant bacteriuria considered to be present only if that dipslide showed a pure growth of $>10^8$ colony-forming units/l. The mean number of urine cultures obtained from each girl over the seven years of follow-up was 30 (range 16-50). The amount of infection experienced by each girl was calculated from the number of infected midstream urine specimens divided by the total number, and this was expressed as a percentage. Statistical analyses were performed with Student's *t* test, *p* values of <0.05 being regarded as significant.

Results

Glomerular filtration rates are expressed in ml/min/1.73 m². Mean values are expressed $\pm$ SD. The mean glomerular filtration rate for the whole group was 112 ± 22 . Figure 1 shows the rates in girls with normal and scarred kidneys, and the data are also presented according to whether or not their kidneys were drained by refluxing ureters. The mean rate in girls with scarred kidneys (99 ± 24) was significantly ($0.005 > p > 0.002$) reduced compared with that in girls with normal kidneys (119 ± 18). In the 25 girls with vesicoureteric reflux the mean glomerular filtration rate (103 ± 21) was reduced compared with the 23 girls in whom no reflux was present (120 ± 20); this difference was significant ($0.01 > p > 0.005$). Only one of the girls with normal kidneys had a glomerular filtration rate of less than 90 compared with five of the girls in the group with renal scarring.

Figure 2 gives the glomerular filtration rates of individual kidneys. The mean filtration rate in scarred kidneys was 31 ± 15 compared with 62 ± 12 in normal kidneys; this difference was highly significant ($0.001 > p > 0.0005$). The presence of vesicoureteric reflux did not influence the glomerular filtration rate in either scarred or unscarred kidneys. The mean rate in 11 scarred kidneys with reflux was 31 ± 18 and in nine scarred kidneys without reflux 30 ± 11 . Again the glomerular filtration rate of normal kidneys drained by refluxing ureters (61 ± 12) was not significantly different from that of normal kidneys drained by non-refluxing ureters (63 ± 12). Figure 3 shows the glomerular filtration rates of normal kidneys drained by refluxing ureters. Kidneys drained by grade 1 refluxing ureters had a mean glomerular filtration rate of 59 ± 5 , which was not significantly different from the rate in kidneys drained by grade 2 (63 ± 15) or grade 3 refluxing ureters (58 ± 8). In eight girls with normal kidneys and

unilateral vesicoureteric reflux the mean glomerular filtration rate was 57 ± 8 on the refluxing side, which was not significantly different from that on the non-refluxing side (56 ± 12).

Tables II and III summarise the effect of duration of infection over the seven years of follow-up. Both normal and scarred kidneys exposed to prolonged infection failed to show a reduction of glomerular

FIG 1—Glomerular filtration rates (GFR) in 48 girls with covert bacteriuria. Bars are means $\pm$ SD.

FIG 2—Glomerular filtration rates (GFR) from 96 single kidneys of 48 girls with covert bacteriuria. Bars are means $\pm$ SD.

filtration rate compared with kidneys exposed to infection for shorter periods, even when these infections were associated with vesicoureteric reflux. Table IV shows the glomerular filtration rates in the treated and untreated groups of girls. Treatment reduced the duration of covert bacteriuria but had no effect on glomerular filtration rate.

The mean glomerular filtration rate of the normal kidneys in 16 girls with unilateral kidney scarring (fig 4) was significantly greater than that of individual kidneys in girls who did not have kidney scarring, thus confirming that compensatory hypertrophy of "opposite" kidneys had occurred. Eight of these opposite kidneys had been exposed to vesicoureteric reflux, and the glomerular filtration rate of these kidneys was not lower than that of the opposite kidneys which had not been so exposed. Similarly the duration of infection did not

TABLE II—Effect of percentage of infected urine specimens and vesicoureteric reflux on glomerular filtration rate (GFR) in 76 radiologically normal kidneys

% Infected specimens during seven-year follow-up	Normal kidneys with vesicoureteric reflux		Normal kidneys with no vesicoureteric reflux	
	Mean GFR (ml/min/1.73 m ²) ± SD	No	Mean GFR (ml/min/1.73 m ²) ± SD	No
0-20	52	1	57 ± 17	10
21-40	72 ± 19	3	64 ± 5	12
41-60	58 ± 18	6	60 ± 6	11
61-80	58 ± 5	7	65 ± 16	10
81-100	66 ± 7	7	67 ± 14	9

TABLE III—Effect of percentage of infected urine samples and vesicoureteric reflux on glomerular filtration rate (GFR) in 20 kidneys with radiological scarring

% Infected specimens during seven-year follow-up	Scarred kidneys with vesicoureteric reflux		Scarred kidneys with no vesicoureteric reflux	
	Mean GFR (ml/min/1.73 m ²) ± SD	No	Mean GFR (ml/min/1.73 m ²) ± SD	No
0-20	31 ± 16	0	39	1
21-40	33 ± 19	3	13	2
41-60	33 ± 19	3	37	2
61-80	30 ± 27	4	34	1
81-100	35	1	34 ± 8	3

TABLE IV—Effect of treatment on glomerular filtration rate (GFR) in 48 girls with covert bacteriuria

	No	Control group		No	Treatment group		No
		Mean GFR (ml/min/1.73 m ²) ± SD	Mean % infected urine samples ± SD		Mean GFR (ml/min/1.73 m ²) ± SD	Mean % infected urine samples ± SD	
All girls	48	113 ± 21	69 ± 22	21	109 ± 24	41 ± 22	27
Girls with scarring	18	104 ± 19	75 ± 18	9	93 ± 28	42 ± 15	9
Girls with normal kidneys	30	123 ± 18	66 ± 24	12	99 ± 30	42 ± 16	7*
					116 ± 17	40 ± 25	18

*Data obtained after excluding two girls with bilateral renal scarring.

influence the glomerular filtration rate of opposite kidneys. Five girls with renal scarring had abnormally low glomerular filtration rates (below 80). Two of these girls, both of whom had a filtration rate of 74, had bilateral renal scarring. Three girls (total filtration rates 59, 63, and 68) had unilateral scarring; filtration rates in the opposite kidneys were 52, 56, and 59. One of these opposite kidneys was drained by a refluxing ureter. Two girls were in the treatment group and had a high proportion of infected urine samples (56% and 64%). The other girl, who was in the control group, had infection in 34% of samples but no documented infection during the three years before estimation of her glomerular filtration rate. Two of these girls had proteinuria exceeding 200 mg/24 hours. All three girls were normotensive.

Discussion

During the past decade there has been considerable interest in screening for covert bacteriuria with a view to preventing kidney failure due to chronic pyelonephritis. Although there is a clear association between bacteriuria, vesicoureteric reflux, and renal scarring, the role of the bacteriuria and reflux in producing kidney damage at different ages and in different clinical situations is not clear. While no one would argue the need to treat children with symptoms, the wisdom and practicality of providing effective long-term or intermittent treatment for symptomless and usually less motivated children and parents are far from clear. It is therefore mandatory to define the relative importance of bacteriuria and vesicoureteric reflux in kidney damage.

By measuring the clearance of technetium-99m-labelled

FIG 3—Effect of grade of vesicoureteric reflux on glomerular filtration rate (GFR) in 24 unscarred kidneys of girls with covert bacteriuria. Bars are means ± SD.

FIG 4—Glomerular filtration rates (GFR) of 16 normal kidneys opposite scarred kidneys in girls with covert bacteriuria and unilateral renal scarring. Bars denote mean GFR ± 2 SD for normal kidneys.

diethylenetriaminepenta-acetic acid we have assessed the effects of bacteriuria, vesicoureteric reflux, and kidney scarring on glomerular filtration rate both separately and in combination. Whereas the total glomerular filtration rate for girls with scarred kidneys was reduced compared with that of girls with normal kidneys, there was considerable overlap between the groups. The filtration rate in individual scarred kidneys was reduced to about 50% of that in the normal kidneys. This emphasises the serious effect of kidney scarring on renal function. When total glomerular filtration rate was considered the effect was partially masked by compensatory hypertrophy of the contralateral kidney.

In this study micturating cystography had been carried out three to four years before the determination of glomerular filtration rate, and in the intervening period vesicoureteric reflux may have cleared spontaneously in some subjects. Nevertheless, our findings show that vesicoureteric reflux of at least four years' duration did not influence the glomerular filtration rate either in scarred or in normal kidneys and that half of the kidneys showing compensatory hypertrophy had been drained by refluxing ureters for the same period. Furthermore, normal kidneys exposed to grade 3 reflux, which is unlikely to disappear spontaneously, did not show a reduction of glomerular filtration rate, and in cases where unilateral reflux had been present the affected side did not have a lower rate than the normal side. Hence vesicoureteric reflux alone does not appear to influence glomerular filtration rate. The reduction in total glomerular filtration rate in girls with vesicoureteric reflux is therefore accounted for by the large number of scarred kidneys in this group rather than the presence of reflux. If we assume that kidney function and growth are interrelated our findings accord with the observations of Smellie *et al.*,¹⁸ who showed that kidney growth in children with symptomatic urinary tract infection was not influenced by the presence or severity of vesicoureteric reflux.

Aperia *et al.*¹⁹ determined glomerular filtration rates in bacteriuric children using the clearance of inulin as a measure. They also studied individual kidney function by using external ureteric compression. Aperia *et al.* found a reduced glomerular filtration rate in kidneys drained by grade 3 refluxing ureters which became more noticeable with age. They did not, however, analyse the data with respect to renal scarring, which may well account for the discrepancy between their findings and ours. Wikstad *et al.*²⁰ described a reduction in the area of the renal parenchyma in kidneys drained by grade 3 refluxing ureters in children aged 4 months to 13 years. Five of the eight children studied developed scarring during the four years of observation, and in two patients a relative decrease in kidney size was thought to be due to a failure of kidney growth. The high incidence of progressive scarring in that study may have been related to the younger age of the patients compared with the girls included in our series, for urinary tract infection and vesicoureteric reflux in combination are known to be most damaging to the kidneys before the age of 4.

In our study prolonged bacteriuria was not associated with a reduction of glomerular filtration rate in girls over the age of 4 and no benefit from intermittent antibiotic treatment was shown. In girls with scarred kidneys who might have been expected to have progressive renal damage there was no difference in function between the kidneys exposed to severe vesicoureteric reflux or prolonged infection, or both, and those not exposed to these conditions. Since we found no relation between the duration of urinary tract infection and glomerular filtration rate it is not surprising that our treatment did not benefit kidney function. These results differ from the data of Smellie *et al.*,¹⁸ who showed in uncontrolled studies that long-term prophylaxis of symptomatic infections benefited kidney growth. It may be that the findings of Smellie *et al.* differ from ours because they were treating children with symptomatic infections, which are presumably caused by more virulent pathogens than those encountered in symptomless infections. It is also possible that the long-term treatment used by Smellie *et al.* achieved better eradication of bacteria than the short courses of treatment employed in our study. It should be borne in mind, however,

that long-term antibacterial prophylaxis of symptomless infections is unlikely to succeed since motivation to comply with such treatment is difficult to achieve. From our findings it is unlikely that treatment of covert bacteriuria whether short or long term will be beneficial or that the incidence of end-stage kidney failure will be influenced by screening for bacteriuria after the age of 5 years.

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MEDICINES APPROPRIATED TO THE HEAD—By [head] is usually understood all that part of the body which is between the top of the crown, and the uppermost joint of the neck, yet are those medicines properly called *Cephalical*, which are appropriated to the brain, not to the eyes, ears, nor teeth; neither are those medicines which are proper to the ears, proper also to the eyes, therefore (my intent being to write as plain as I can) I shall subdivide this chapter into these parts. Medicines appropriated 1. *To the brain*. 2. *To the eye*. 3. *To the mouth, and nostrils*. 4. *To the ears*. 5. *To the teeth*. For what medicines are appropriated to an unruly tongue, is not in my power at present to determine. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)