Age as a main determinant of renal functional damage in urinary tract infection

U B BERG AND S-B JOHANSSON

Department of Paediatrics, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden

SUMMARY Renal function was studied in 61 girls suffering from recurrent urinary tract infections, with at least one febrile infection. Clearance of inulin was determined. Intravenous urography and micturating cystourethrography were performed 1-6 months after the first infection and 0-6 months before or after the function test. A low glomerular filtration rate (GFR) was found only among children with their first pyelonephritis before the age of 3 years. A low GFR was found mostly in patients with small or scarred kidneys but was also seen in a few patients with normal intravenous urographs. Low GFR as well as radiologically small kidneys at the time of the function test were found independently of the presence or grade of vesicoureteral reflux at first infection. Patients with early onset pyelonephritis (before age 3 years) had a low capacity for early compensatory hypertrophy in contrast to patients with late onset pyelonephritis.

Three percent of all girls contract a symptomatic urinary tract infection (UTI) before the age of 11 years.¹ Half of them will have recurrences and 5-10% of them will develop renal scarring.^{1,2} Only a few children with UTI will, however, progress to renal insufficiency. Because of the high risk of recurrence and the risk of renal scarring, large resources are allocated to the follow up of all girls after their first UTI. It is therefore desirable to identify those girls at risk of developing renal damage. Our aim was to study renal function in children with recurrent UTI and to detect those patients at high risk of developing renal function damage.

Patients and methods

Sixty one girls, 1.5-15 years of age, were studied. All girls had had recurrent, symptomatic bacteriologically proved UTI. The height and weight of the girls were within normal limits for Swedish children.³ At least one infection had been febrile (fever >39°C) with an erythrocyte sedimentation rate (ESR) >20 mm/hr suggesting renal involvement.⁴ When infected, the children had received treatment for 7-10 days with an appropriate antibacterial drug, and several had received low dosage prophylaxis with nitrofurantoin or co-trimoxazole for at least 6 months. Bacteriological and clinical follow up continued every two-three months during follow up.

All patients had been investigated radiographically with intravenous urogram (IVU) and micturating cystourethrography (MCU) at least twice: once 1-6 months after the first or second infection and then 0-6 months before or after renal function was tested.

Renal length was measured and related to the L1-L3 distance according to Eklöf-Ringertz.⁵ Renal parenchymal area was calculated planimetrically according to the method of Aperia *et al.*⁶ It was related to the L1-L3 distance and the nomogram of Jorulf *et al.*⁷ Renal parenchymal thicknesses were measured in the upper and lower pole as well as in the lateral aspect of each kidney and were related to the nomogram of Claesson *et al.*⁸ Vesicoureteral reflux (VUR) was graded according to a three point scale. Grade 1, reflux into the ureter not extending up to the renal pelvis; grade 2, reflux extending up to the renal pelvis but without dilatation; and grade 3, reflux extending up to the renal pelvis including ureteral or pelvic dilatation, or both. Renal function was determined by clearance of inulin⁹ expressed as the glomerular filtration rate (GFR). A standard clearance technique was used including continuous infusion of inulin. Water diuresis was induced enabling the patients to empty their bladders by spontaneous voiding every 30 minutes. Four sampling periods were used, and the clearance values presented are the mean values of the four periods. No patient had bacteriuria during

the three months immediately before the function test. Blood and urine samples were analysed for inulin by the anthrone method.¹⁰

The clearance data were compared with those of 13 controls. Three of the controls were young adult kidney donors, three were healthy young adult volunteers, and 7 were children 5–13 years of age. Four of these 7 children had nocturnal enuresis without bacteriuria and with a normal IVU—one child had psychogenic polydipsia, and one was investigated because of suspected hypertension, which could not be verified. The last child had a raised serum creatinine value that was found to be caused by a technical fault in the laboratory analysis. The GFR in this control group was mean (SD), 114 (11) ml/min/1.73 m². In addition, 13 girls aged 7–15 years, with a clinical history of recurrent lower UTI without fever and with a normal ESR as well as a normal IVU and MCU were investigated by the same clearance technique. The GFR of these girls was mean (SD), 116 (9) ml/min/1.73 m², confirming the normality of the control group.

Data are given as mean (SD). Student's *t* test was used for statistical analysis. All the children and their parents gave their informed consent and the study was approved by the ethical committee of the Karolinska Institute.

Results

Radiological findings. The radiologist's findings on the IVU and the MCU of all patients when first and last investigated are given in Tables 1 and 2.

Renal function. The individual GFR values related to the age of the patients at the time of the function test are shown in Fig. 1. Twenty of the 61 girls had a GFR less than -2 SD of that of controls. Fig. 2

Table 1 Intravenous urogram findings in 61 girls with urinary tract infections investigated after the first or second infection, and at the time of renal function test

	After infection No	At study No
Normal sized kidneys* without parenchymal reduction	42	23
Normal sized kidneys* with parenchymal reduction	9	17
Small† kidney(s) without parenchymal reduction	5	1
Small† kidney(s) with parenchymal reduction	5	20

*Renal length within ± 2 SD according to Eklöf *et al.*⁵

†Renal length(s) < -2 SD according to Eklöf *et al.*⁵

Table 2 Micturating cystogram findings in 61 girls with urinary tract infections investigated after the first or second infection and at the time of renal function test

	After infection No	At study No
No VUR	26	38 (5 after operation)
Moderate VUR	17	13
VUR with dilatation	18	10

VUR = vesicoureteral reflux.

Fig. 1 Glomerular filtration rate (GFR) of each patient in relation to her age at the time of the renal function test. The dotted lines indicate ± 2 SD of control value.

Fig. 2 Glomerular filtration rate (GFR) of each patient in relation to her age at the first pyelonephritis (PN). The dotted lines indicate ± 2 SD of control value.

shows the individual GFR values in relation to the stratified age (each strata = 6 months) of the patients when having their first verified febrile infection (pyelonephritis (PN)). Only those patients with early onset PN (before the age of 3 years) had a low GFR. The patients were therefore grouped into those with early onset PN (PN < 3 years) and those with late onset PN (PN > 3 years). The GFR among the 34 patients with early onset PN was mean (SD), 86 (20) ml/min/1.73 m² with the three lowest GFR values included, and 91 (11) ml/min/1.73 m² with those three excluded. Both mean values were significantly lower than that of controls (P < 0.001). The GFR among the 27 patients with

late onset PN was mean (SD), 109 (8) ml/min/1.73 m², which did not differ from that of the controls.

In Fig. 3 the GFR values are given in relation to the girls' age at UTI (febrile or not) and when functionally tested. Some of the patients with late onset PN had had a lower UTI before the first febrile attack. There was no difference in the mean age of the patients in the two groups when renal function was tested (8.8 and 9.6 years respectively). Few patients had passed puberty. The mean follow up time from the first febrile infection to the renal function test was 7.4 years in the early onset PN patients and 3.9 years in the late onset PN patients. Except for the three patients with a severely reduced GFR, there was no sign of decreasing GFR with increasing follow up time. The mean number of febrile attacks in the two groups were four and three respectively.

Renal function in relation to radiological findings.

Filtration rate in relation to MCU findings

Fig. 4 shows the individual GFR values in relation to the grade of VUR in those 45 girls who underwent radiography after their first PN. Only two girls with late onset PN had VUR with dilatation. In the patients with early onset PN no relation was seen between the GFR and the grade of VUR. A low GFR was thus found independently of the presence or grade of VUR at the time of the first PN. In Fig. 4 the GFR values are all total and do not

Fig. 3 The clinical picture during the follow up of each patient in relation to age and glomerular filtration rate.

↓ Indicates a febrile UTI, + indicates a lower UTI or asymptomatic bacteriuria, and ▽ indicates operation for VUR. The dashed lines show periods of time when the patient was lost to follow up.

Fig. 4 Total glomerular filtration rate (GFR) of each patient in relation to grade of vesicoureteral reflux in 45 girls investigated radiographically at the first pyelonephritis (PN). The dotted lines indicate ± 2 SD of control value.

differentiate between the two kidneys. Since it has been shown that there is good correlation between renal surface area and renal function,⁶ the renal surface area of each kidney was estimated planimetrically. On the basis of the percentual distribution of renal surface areas of each kidney and the total GFR values, the GFR of each kidney was calculated. Again no relation was found between GFR and grade of VUR (Fig. 5).

Nine ureters of five patients with grade 3 refluxes had been operated upon. The GFR of those 9 kidneys was mean (SD), 44 (13) ml/min/1.73/m² which did not differ from the GFR mean (SD), 40 (16) ml/min/1.73/m² of those kidneys with grade 3 refluxes that were not operated upon.

In several patients VUR had disappeared when the function tests were performed and no relation could be found between GFR of each kidney and its grade of reflux at the time of the function test.

Filtration rate in relation to IVU findings

In order to evaluate whether the IVU findings at the time of the function test could predict the reduced GFR, the renal surface area (RSA) was planimetrically measured. Patients were divided into two groups—(1) those with one or two small kidneys (RSA ≤ -2 SD and (2) those with RSA > -2 SD (Fig. 6). The GFR in group 1 among early onset PN girls (n=18) was mean (SD), 80 (24) ml/min/1.73/m² and among early and late onset PN girls (n=23) was 86 (25) ml/min/1.73/m², while corresponding values in group 2 were 93 (12) (n=16) and 102 (13) ml/min/1.73/m² (n=38) respectively. Thus the GFR was lower in those girls with one or two small kidneys.

Parenchymal reduction on the IVU performed at

Fig. 5 Glomerular filtration rate (GFR) of each kidney in relation to grade of vesicoureteral reflux in the 45 girls investigated radiographically at the first pyelonephritis (PN). The dotted lines indicate ± 2 SD of control value.

Fig. 6 Glomerular filtration rate (GFR) in all patients, grouped into those with one or two kidneys with renal surface area (RSA) < -2 SD and those with renal surface areas > -2 SD at time of function test. The dotted lines indicate ± 2 SD of control value.

the time of the function test was evaluated by measuring three local parenchymal thicknesses (called 'zones'), according to Claesson.⁸ Of 48 patients with parenchymal reduction, 20 had bilateral changes, 14 patients had changes in the right, and 14 in the left kidney. The patients were divided into three different groups—(1) those with no parenchymal reduction, (2) those with 1–3 measured parenchymal thicknesses below -2 SD, and (3) those with 4–6 parenchymal thicknesses below -2 SD (Fig. 7). Most patients with a low GFR had some parenchymal reduction.

Among the 20 patients with a low GFR, 7 had an abnormal IVU (according to the radiologist) when first investigated (Table 1). In two of the 7 one or both kidneys were small with parenchymal reduction, in three one or both kidneys were small without parenchymal reduction, and two had normal sized kidneys with parenchymal reduction. In all patients in whom one or both kidneys were small when first investigated, the kidneys had further decreased in relative size on the follow up IVU. Thirteen patients with a low GFR had a normal IVU when first investigated.

Renal size in relation to grade of VUR and to age at first infection

The relation between grade of VUR at first PN and renal surface area at time of function test is shown in Fig. 8 in the 45 girls investigated radiographically after their first PN. Small kidneys could be seen not

Fig. 7 Glomerular filtration rate (GFR) of each patient in relation to grade of parenchymal reduction at time of function test. The patients are divided into three groups—(1) those without parenchymal reduction (zones ± 2 SD), (2) those with 1–3 parenchymal thicknesses < -2 SD (1–3 zones < -2 SD), and (3) those with 4–6 parenchymal thicknesses < -2 SD (4–6 zones < -2 SD). The solid lines indicate the mean GFR in each group. The dotted lines indicate ± 2 SD of control value.

only among patients with gross refluxes but also among patients without any evident VUR at first infection. Small kidneys were also found among the patients with late onset PN.

The capacity of compensatory hypertrophy in patients with early and late onset PN is illustrated in Fig. 9. The renal surface area of the smallest kidney has been related to the renal surface area of the contralateral kidney. In the early onset PN patients, the mean size of the smallest kidney was -2.3 SD while the mean size of the contralateral kidney was $+0.2$ SD. In the late onset group, however, the mean size of the smallest kidney was -1.3 SD and the mean size of the contralateral kidney was $+1.2$ SD, indicating a good capacity for compensatory hypertrophy in contrast to the patients with early onset PN. In the early onset PN patients the GFR values of the smallest and contralateral kidneys were mean (SD), 36 (11) and 50 (12) ml/min/1.73m², respectively, while in the late onset PN patients the corresponding GFR values were mean (SD), 46 (9) and 62 (8) ml/min/1.73m².

Fig. 8 Size (in SD) of each renal surface area (RSA) related to the L1–L3 distance at the time of the function test, in relation to grade of reflux at first investigation. The dotted lines indicate the normal variations.

Fig. 9 The size of renal surface area (RSA) of the smallest kidney related to that of the contralateral kidney in the patients with early and late onset pyelonephritis (PN). The size is expressed in SD when renal surface area is related to the L1–L3 distance. The stars indicate the mean values.

Discussion

Since this study was designed to detect patients at risk of developing renal damage, we selected patients suffering recurrent UTI with at least one febrile infection. The indications for performing function tests were abnormal IVU findings or frequent recurrences. The GFR was reduced in one third of the patients studied. Three patients who had a severely reduced GFR had all been lost to clinical follow up for a period of a few years. A reduced GFR in children with recurrent UTI has previously been found.^{11 12}

All patients with a low GFR in this study had had their first PN before the age of 3 years, around half of them during the first year of life. In previous studies^{13 14} an increased risk of developing renal scarring was found among patients with their first PN during the first year of life. Hodson¹⁵ showed that renal scarring appeared mostly before the age of 6 years.

In most patients with a low GFR in this study, one or both kidneys were small or there was parenchymal reduction, or both. These findings are in agreement with those of Aperia⁶ who found a direct correlation between renal surface area and GFR in patients with recurrent UTI. Four of 21 patients with a low GFR in this study had, however, been considered to have a normal IVU by the radiologist at the time of the function test. Thus a normal radiological finding cannot exclude functional disturbances.

Neither presence nor grade of VUR at first PN was found to be predictive of the later development of renal dysfunction. Not even when the GFR of individual kidneys was calculated was a relation to grade of VUR found. These results seem to contradict those of Aperia *et al.*¹⁶ who studied GFR by separate clearance technique in 22 girls with recurrent UTI, most of whom had a gross, unilateral VUR. Renal function was unaffected when VUR was moderate, small, or non-existent. Those kidneys with no VUR were, however, all contralateral to grade III refluxing kidneys and might therefore have been stimulated to compensatory hypertrophy. Our results are more in agreement with those of Verrier Jones *et al.* who studied schoolgirls with covert bacteriuria and found a reduction in GFR related to loss of kidney substance rather than to VUR.¹⁷ Furthermore, in the present study no difference in GFR was found in kidneys with gross VUR, whether or not they had been operated upon.

Radiologically small kidneys at time of the study were found irrespective of the presence or grade of VUR at first PN. Renal scarring in non-refluxing

kidneys has also been shown by others.^{13 18–20} Small kidneys were found even among patients with late onset PN, but all these patients had a normal total GFR. Thus, there must be some important difference between the infections in patients with early and late onset PN.

It has been shown in rats that infection produces impairment of compensatory hypertrophy.^{21 22} In our patients with early onset PN the capacity of early compensatory hypertrophy was impaired. This insufficient compensation suggests that patients with early onset PN may often have bilateral infections. The capacity of compensatory hypertrophy was greater in patients with late onset PN which may indicate that these patients had mostly had unilateral PN. Additional support for bilateral infections in patients with early onset PN is that among 15 patients with this and a gross VUR at first investigation, 10 had a gross bilateral VUR. Since most patients had not passed puberty when being studied the final compensatory growth spurt²⁰ had not been evaluated.

Another reason for renal dysfunction found among patients with early onset PN is the diagnostic difficulty in this group. These patients often present with high fever and no specific symptoms of UTI,¹ thereby delaying the start of treatment. In human as well as in experimental PN a delay in treatment has been shown to increase the risk of renal scarring.^{20 23 24}

In conclusion, a low total GFR was found only among patients with early onset PN (before the age of 3 years) and was probably caused by bilateral renal involvement impairing the capacity for compensatory hypertrophy. A low GFR was found not only among patients with gross VUR but also among those without any evident VUR. The clinical implication of this study is that the greatest efforts should be allocated to very young children with PN so that an early diagnosis and start to treatment to prevent future renal damage may be made. All these patients must also be followed up thoroughly even if they have a normal IVU and no evident VUR when first investigated radiographically.

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Correspondence to Dr Ulla Berg, Department of Paediatrics, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

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