PAPERS

Development of hypertension and uremia after pyelonephritis in childhood: 27 year follow up
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Abstract

Objective—Determination of the long term incidence of uremia, hypertension, and toxemia in pregnancy associated with non-obstructive focal renal scarring after pyelonephritis in childhood 25-35 years earlier.

Design—27 Year follow up of patients with non-obstructive focal scarring identified from a retrospective review of intravenous urograms performed in childhood between 1951 and 1967.

Setting—Paediatric primary referral centre and urological clinic in tertiary referral centre.

Patients—30 Patients (mean age 33 (range 22-41)) with non-obstructive focal scarring first detected between 1951 and 1967 and a history of febrile urinary tract infection.

Main outcome measure—Hypertension and complications of renal damage.

Results—Three patients had developed end stage renal disease, seven had developed hypertension, two of 16 women had a history of toxemia during pregnancy, and seven patients had undergone renal surgery during follow up. Of the 20 patients who had neither had renal surgery nor had end stage renal disease, all had a significantly lower glomerular filtration rate and renal plasma flow and higher diastolic blood pressure, mean arterial blood pressure, plasma renin activity, and serum ß₂-microglobulin concentration than 13 healthy age matched controls. Diastolic blood pressure and plasma renin activity were positively correlated (r=0.50, p<0.05) and so were fractional sodium excretion and both systolic and diastolic blood pressures (r=0.54, p<0.01, r=0.51, p<0.01 respectively). The progress of renal damage was unrelated to the incidence of recurrent infections.

Conclusions—Children with focal renal scarring due to pyelonephritis are at high risk of serious long term consequences. It is essential that they are given adequate attention and care during adolescence and pregnancy.

Introduction

Chronic atrophic pyelonephritis is a main cause of sustained hypertension and renal insufficiency in children and young adults. As the inflammatory reaction is minimal in this stage of the disease process postinfectious focal renal scarring is a more appropriate descriptive term. The main factors predisposing to the initiation of a focal scar are well known: young age (<3-4 years), virulent bacterial strains, delay between onset of infection and start of antibiotic treatment, and severe vesicoureteric reflux with intrarenal reflux. Because of this last association the condition is also called reflux nephropathy. As it highlights only one of the main predisposing factors and reflux is not always present the term reflux nephropathy is less accurate.

Hypertension and uremia are the two most serious complications of scarring due to pyelonephritis. The mechanisms responsible for the progressive deterioration in kidney function in some patients with focal renal scarring are not understood. Proteinuria is an important predictor for progression to end stage renal disease indicating that glomerular lesions play an important part. The incidence of hypertension in children with focal scarring has been reported as more than 10%. The aetiology of the hypertension is thought to be predominantly renin-angiotensin mediated and is not thought to be volume dependent.

Management of children with focal renal scarring includes effective antibiotic treatment of symptomatic recurrent infections, careful long term follow up to detect and treat hypertension early, and obtaining information about possible subsequent hazards associated with pregnancy. Little information is available on the outcome in children with an early diagnosis of focal renal scarring who have been followed up for decades. In this long term follow up of children with early verified renal scarring due to pyelonephritis we focus on the incidence of uremia and hypertension and the mechanisms underlying the development of these disorders.

Patients and methods

We reviewed all reports of intravenous urograms (between 900 and 1000) performed at the department of paediatric radiology at the Karolinska Hospital between 1951 and 1967 and selected children with signs of non-obstructive focal renal scarring. Children with signs of obstructive malformations on intravenous urography or with compromising diseases—for example, diabetes mellitus—were excluded. This left 53 patients who fulfilled our criteria of focal renal scarring, which was defined as signs of caliceal distortion and retraction of papillae with segmental reduction of parenchyma directly overlying clubbed calices. We studied all radiographs and all available hospital charts of these 53 patients, all of whom had a history of febrile urinary tract infections. Forty seven of the patients could be traced through the Swedish Central Bureau of Statistics, and all were alive. The fate of the remaining six patients is unknown. Thirty of the 47 patients (26 women and four men), now young adults living in different parts of the country, agreed to participate in the study. The mean age when the first urogram was performed was 6 years (range 1-13 years) and at follow up was 33 years (22-41 years). The extent of renal scarring was classified according to Smid et al. Of the 60 kidneys that had been examined in childhood three were classified as type a (mild scarring), 12 as type b (severe scarring), 22 as type c (back pressure scarring), three as type d (end stage kidney), and 20 were normal. Nineteen children (63%)
had unilateral renal scarring, and 11 (37%) had bilateral scarring; in all patients scarring was evident in the first urogram. Voiding cystourethrography had been performed in 26 children; 21 (81%) had, according to the original report from 1951 to 1967, reflux to the renal pelvis and five (19%) had no reflux or only minor reflux not reaching the pelvic region (the radiographs had not been saved and could thus not be reviewed). No systematic studies of blood pressure and renal function had been performed in these patients during childhood.

We interviewed the patients carefully, focusing on the frequency of urinary tract infections during childhood and adolescence, complications during pregnancy, control of blood pressure, and development of proteinuria. Three patients had developed end stage renal disease; the remaining 27 had tests for renal function including determination of glomerular filtration rate; renal plasma flow; renal blood flow; filtration fraction; fractional excretion of sodium and potassium; serum β2 microglobulin concentration; urinary excretion of β2 microglobulin and albumin; plasma renin activity; and plasma angiotensin II, aldosterone, and antidiuretic hormone concentrations. All drugs including antihypertensive drugs were withdrawn seven days before the tests. Ten women and three men, mean age 34 (range 25-41), all volunteers from this hospital with normal kidneys on recent intravenous urography and without a history of symptomatic urinary tract infections were included as healthy controls.

### Tests for Renal Function

Glomerular filtration rate was measured as the clearance of inulin and renal plasma flow as the clearance of p-aminohippurate both in terms of their rate/minute and corrected to 1-73 m2 body surface area. The subjects received 0-5 ml/kg body weight of a solution containing 85 g/l of inulin (Inutest) and 30 g/l of p-aminohippurate (Merck Sharp and Dohme) as a loading dose. The solution was then infused intravenously by a motor driven syringe at the constant rate of 0-3 or 0-5 ml/minute depending on renal function. The equilibrium time was 60 minutes. All patients were studied during three 30 minute periods. Blood samples were taken from an antecubital vein at the middle of each period. Urine was collected at the end of each control period. Concentrations of inulin and p-aminohippurate in serum and urine were determined as previously described. Renal blood flow was calculated as renal plasma flow/(1-packed cell volume) and the filtration fraction was calculated as the ratio of the glomerular filtration rate/renal plasma flow and expressed as a percentage. Fractional clearances of sodium and potassium were calculated in relation to the clearance of inulin. All patients gave informed consent, and the study was approved by the ethics committee of this hospital. All patients were examined by the same nurse.

Systolic and diastolic blood pressures were recorded in the left arm after five minutes' rest with the patients recumbent. Mean arterial blood pressure was calculated as diastolic pressure plus one third of the (systolic-diastolic pressure).

The urinary albumin excretion was determined with a solid radioimmunoassay technique, and serum and urine β2 microglobulin concentrations were determined with a radioimmunoassay kit with iodine-125 (Phadebas, Pharmacia Diagnostics). Plasma renin activity was measured with a radioimmunoassay kit with [125I] for angiotensin I (New England Nuclear, United States) in each subject after resting for one hour in the recumbent position. Plasma concentrations of angiotensin II and antidiuretic hormone were determined by radioimmunoassay (Bühlman, Basle), as was aldosterone (Coat a Count, Diagnostic Product Cooperation, United States).

### Statistical Analysis

Results are given as means (SD). For normally distributed data a two tailed Student t test was used, otherwise the Mann-Whitney U test was used for unpaired observations. Pearson's correlation coefficients were determined.

### Results

Information obtained from hospital charts and through interviews at follow up showed that the mean age at the first attack of pyelonephritis (from the paediatic records) was 4 (2-8) years (range 1-11 years). Six patients had their first infection during the first year of life and 11 before the age of 2 years. In the 13 others the onset of pyelonephritis was said to be later. During early childhood 14 of 24 female patients (58%), from whom detailed data were available, had a history of several (five or more) episodes of urinary tract infections with high fever. During adolescence and adulthood 17 of the 30 patients (57%) had had recurrent cystitis, and 14 (47%) had a history of recurrent upper urinary tract infections.

The 30 patients were interviewed and examined after an interval of 27 (6) years. Seven patients had arterial hypertension (>140/90 mm Hg) and in three this was unknown before our follow up. Three patients had developed end stage renal failure at ages 17, 31, and 34; one was receiving maintenance haemodialysis and two had functioning kidney grafts. Six patients had had unilateral nephrectomy and one had a partial nephrectomy. Vesicoureteric reflux had been corrected surgically in 11 patients. Details of radiological findings will be published later.

Three had had two pregnancies in 16 women. There was no appreciable difference in renal function or blood pressure control between the women who had been pregnant and the women who had not. During pregnancy three of these women had had symptomatic urinary tract infections, two had had toxemia (proteinuria, excessive oedema, and hypertension), and four patients had had proteinuria (positive result on dipstick testing). No fetuses had been lost.

Follow up examinations to assess renal function and control of blood pressure were performed in the 27 patients who did not have end stage renal failure. Renal function—The mean glomerular filtration rate of these patients, who all had renal scarring, was 90 (17) ml/min/1-73 m2 compared with 108 (12) ml/min/1-73 m2 for the 13 healthy controls (p=0-014). Renal plasma flow and renal blood flow were significantly lower in patients than in controls (469 (99) ml/min/1-73 m2 v 587 (89) ml/min/1-73 m2 and 761 (180) ml/min/1-73 m2 v 989 (151) ml/min/1-73 m2, respectively, p<0-01). Control of blood pressure—Diastolic and mean arterial blood pressure were significantly higher in the patients than in the controls (83 (11) mm Hg v 72 (8) mm Hg and 97 (12) mm Hg v 86 (7) mm Hg respectively, p<0-01). There was no significant difference in systolic pressure.

Plasma renin activity and plasma angiotensin II, aldosterone, and antidiuretic hormone concentrations—Plasma renin activity was higher in patients than in controls (0-99 (0-69) nmol/l/h v 0-61 (0-22) nmol/l/h, p=0-064). There were no significant differences in plasma aldosterone or angiotensin II (37 (4)-(44-7) pmol/l v 20-7 (13-8) pmol/l), aldosterone (295 (202) pmol/l v 229 (127) pmol/l), or antidiuretic hormone (2-79 (1-49) pmol/l v 1-97 (1-13) pmol/l, p=0-088). Fractional sodium excretion was similar in patients and controls, but fractional potassium...
excretion was significantly lower in patients than in controls (21% and 27%, respectively, p = 0.054).

The table summarises the results of the tests for renal function, blood pressure regulating hormones, and other variables for 20 patients who neither had renal surgery nor had end stage renal disease and the 13 controls. The patients with renal scarring had significantly lower glomerular filtration rate, renal plasma flow, and fractional potassium excretion than the controls. Diastolic and mean arterial pressure, plasma renin activity, and serum β2 microglobulin concentration were significantly higher in these patients than in the controls. There were no significant differences in renal function, concentrations of renal hormones, or control of blood pressure among the seven patients who had had renal surgery or nephrectomy and the 20 who had not. There was a significant positive correlation between plasma renin activity and both diastolic pressure (r = 0.50, p < 0.05 (95% confidence interval 78 to 85)) and mean arterial pressure (r = 0.44, p < 0.05 (91 to 99)) in all 27 patients.

Control of blood pressure was not correlated with plasma angiotensin II, aldosterone, or antidiuretic hormone concentrations. A reduction in renal plasma flow was accompanied by a significant increase in diastolic pressure (r = 0.40, p < 0.05 (79 to 87)). Glomerular filtration rate, renal blood flow, or filtration fraction were not, however, correlated with control of blood pressure. Patients with a high fractional sodium excretion had higher systolic pressure (r = 0.54, p < 0.01 (119 to 130)), diastolic pressure (r = 0.51, p < 0.01 (79 to 87)), and mean arterial blood pressure (r = 0.53, p < 0.01 (92 to 101)). A reduction in glomerular filtration rate was accompanied by an increase in albumin excretion (r = 0.40, p < 0.05 (3.4 to 10.3)).

Renal function, concentrations of renal hormones, and control of blood pressure were not significantly different among patients who had had their first clinical episode of pyelonephritis before or after 2 years of age, patients with or without severe reflux, those with or without a history of recurrent infections during adolescence, or with unilateral versus bilateral primary renal damage.

**Discussion**

The present study describes the long term prognosis in patients who sustained unilateral or bilateral renal scarring after pyelonephritis in childhood.

Renal damage was already present in all 30 patients when the first urogram was performed during childhood, but there was little to suggest that the damage was congenital. Three patients had since developed end stage renal disease, and seven had developed hypertension during early adulthood. Our follow up disclosed earlier unknown hypertension in three of the patients. Two women out of 16 had toxæmia of pregnancy and another four had proteinuria during pregnancy. The incidence of toxæmia in Sweden is much lower. If the prognosis for this group of patients is representative for comparable children becoming ill during the 1940s and 1950s it would mean that renal scarring in a child of that time may have been associated with a 10% risk of having uræmia, an additional 13% risk of developing hypertension, and a 13% risk of having toxæmia. These figures might increase during a prolonged follow up. Hodgson and Wilson reported that the age related incidence of focal renal scarring was maximal between 15 and 20 years of age and then decreased, concluding that this might be due to a decreased mortality among young adults with renal scarring. Our findings support this speculation.

Though the first infection in most of our patients had not been recognised and adequately treated, their subsequent care was usually good considering that available treatment is probably not greatly progressed. That the incidence of recurrent urinary tract infections during childhood was not correlated with the degree of loss of renal function observed in adulthood suggests that renal damage once established in early life may progress whatever care is given, provided that symptomatic infections are treated promptly and hypertension is well controlled. This accords with earlier studies. In patients with renal scarring due to pyelonephritis receptors for pyelonephritic *Escherichia coli* strains are more accessible and the incidence of cystitis and acute pyelonephritis is high. This may be important in long term outcome.

Scarring due to pyelonephritis is the commonest cause of hypertension in childhood, and its incidence in patients with reflux nephropathy has been estimated at over 11%, which compares well with our findings. A lack of correlation between blood pressure and degree of functional impairment and loss of parenchyma has been reported. The significant positive correlation between plasma renin activity and diastolic pressure accords with previous observations but contradicts the findings of Savage et al. The increase in serum β2 microglobulin concentration in that study was probably secondary to the reduction in glomerular filtration rate. Mean albumin excretion was not increased (table) in our patients, but the patient with the lowest glomerular filtration rate (55 ml/min/1.73 m²) had proteinuria (urinary protein concentration 115 mg/l), which accords with observations by Kincaid-Smith. The incidence of complications during pregnancy is increased in patients with pyelonephritis. In Australia and the United Kingdom studies have shown a higher incidence of pre-eclampsia, hypertension, and urinary infections in patients with reflux nephropathy than in our study; in addition fetal loss was common.

Experience during the past two to three decades suggests that the risk of severe renal damage after acute urinary infections is greater during the first two years of life than later. In industrialised countries this is now recognised, and such infections in most children will be diagnosed and treated promptly and followed up. In less affluent societies acute pyelonephritis probably still often leads to severe renal damage and may be a major cause of hypertension and renal failure in adolescence and early adulthood. Our study shows...
Collected and neglected: Are Oxford hostels for the homeless filling up with disabled psychiatric patients?

Max Marshall

Abstract

Objective—To assess the severity of psychiatric symptoms among residents of hostels for homeless people.

Design—Survey of residents in two hostels in Oxford, comprising three weeks of background fieldwork, a demographic questionnaire, and rating behaviour over two weeks with a behavioural rating scale (REHAB) and mental state with the brief psychiatric rating scale.

Setting—Two hostels for homeless people in Oxford

Subjects—146 Medium to long term residents, of whom 48 were selected by hostel workers by the following criteria: continuous residence for at least two months, signs of persistent severe mental disability, and difficulty in coping independently in the community. Two subjects died during the study; three (previously long term psychiatric inpatients) declined to be assessed on the psychiatric scale.

Main outcome measure—Behavioural disturbance and mental state.

Results—Only a third of the total sample had been born in Oxfordshire. Subjects had been accepted into the hostel either by arrangement with the local psychiatric service (22) or straight off the streets (26); 43 had had a previous (non-drug related) psychiatric admission. Subjects were significantly more likely than other residents to have spent longer (>80 weeks) in a hostel in the past three years (p<0.02). With reference to norms for deviant behaviour, the 46 subjects assessed showed considerable deviant behaviour (average weekly scores: 0 (11 subjects), 1 (14), 2-3 (16), and ≥4 (5)) not significantly different from that expected in moderately to severely handicapped psychiatric inpatients (p=0.1-3, df=3, p=0.7); 22 had scores equivalent to those in most severely handicapped inpatients. Of the 43 subjects assessed with the psychiatric rating scale, 16 had symptoms of neurosis, 29 of florid psychosis, and 32 of a deficit state. Symptoms of deficit state were positively correlated with ratings of low social activity on the behavioural scale (Spearman’s rank correlation coefficient 0.30, p=0.003).

Conclusions—Hostels are having to care for long term severely affected psychiatric patients discharged into the community. The suitability of the services offered to such subjects should be assessed.

Introduction

The presence of mentally disordered “street people” in every major town and city alerted the public in the United States to the unforeseen deficiencies of an ambitious programme of deinstitutionalisation. Surprisingly, although a similar and no better planned policy has been adopted in Britain, equivalent numbers of conspicuously mentally ill people do not seem to be living on the streets. This might reflect a cultural difference, in that homeless mentally ill people in

References


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