CLINICAL RESEARCH

Renal function in patients over 40 with homozygous sickle-cell disease

A G MORGAN, G R SERJEANT

Abstract

Renal function was examined in 25 patients aged 40-64 with homozygous sickle-cell (SS) disease. Investigations included intravenous urography and measurement of blood urea and creatinine concentrations and creatinine and protein excretion in 24-hour collections of urine.

Serum creatinine concentrations did not differ significantly from those of 25 other patients with SS disease aged 18-39 years, but serum urea concentrations were significantly higher ($p < 0.001$). Intravenous urography showed loss of caliceal cupping (nine patients), irregular renal outline (five), and cystic extension from the calix (one). Six patients had creatinine clearances below the fifth percentile for age and sex. Proteinuria was more common in these patients, and haemoglobin concentrations were much lower than in the 19 patients without renal insufficiency (mean 5·6 v 8·2 g/dl; $p < 0.001$). Haemoglobin concentration was strongly correlated with creatinine clearance ($r = 0.70$), particularly with clearances below 100 ml/min/1·73 m^2 ($r = 0.96$; $p < 0.001$).

A possible mechanism of renal insufficiency in SS disease is cortical scarring, which is asymptomatic, not associated with hypertension, and accompanied by only minor proteinuria. A falling haemoglobin concentration is a sensitive and early indicator of renal impairment in SS disease.

Introduction

Damage to the renal medullary blood supply compromises renal tubular function early in homozygous sickle-cell (SS) disease[1] but glomerular function is usually well maintained. In children and young adults glomerular filtration rates exceed normal[2] but may fall at later ages.[3] The contribution of deteriorating glomerular function to morbidity and mortality in older patients with SS disease[4] is not widely recognised. It is a clinical impression that renal failure is common in such patients in Jamaica, and a necropsy survey of the University Hospital of the West Indies indicated that renal failure contributed to or caused death in 11 out of 49 (22%) patients aged over 30 years (unpublished observations). We report renal function in 25 unselected patients aged 40 years or over.

Patients and methods

Among patients attending the sickle-cell clinic of the University Hospital of the West Indies in a six-month period there were 25 (12 men, 13 women) aged 40-64 years who consented to this study. The diagnosis of SS disease was based on a single major haemoglobin (Hb) band in the position of HbS on cellulose acetate and agar-gel electrophoresis, compatible HbA_2 concentrations, and family study where possible. All patients were admitted to a metabolic ward for four days, and none had been given a blood transfusion in the preceding four months.

Routine haematological procedures were used. Other investigations included intravenous urography after overnight fluid restriction, bacteriological examination of midstream urine, measurement of blood electrolyte, urea, and creatinine concentrations, and two 24-hour urine collections for creatinine and protein excretion. The mean of two determinations of creatinine clearance was corrected for surface area derived from height and weight. Routine parametric statistical procedures were used, and the skewed distributions of serum urea and creatinine were corrected by log transformation before further analysis.

Results

CLINICAL

Twenty-four patients denied acute symptoms, though 16 had mild breathlessness on exertion. One 64-year-old woman with known renal failure had severe effort dyspnoea intermittently relieved by transfusion. Other clinical features were compatible with SS

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disease. All patients took analgesics (usually paracetamol) but none exceeded 10 tablets monthly.

Physical examination showed cardiomegaly in all cases; ejection systolic murmurs were common, and the jugular venous pulse was raised in two. No patient was hypertensive, and blood pressure was generally low for age (mean 117 ± SD 9 mm Hg systolic, 65 ± 7 mm Hg diastolic). In no patient were the kidneys palpable.

HAEMATOLOGICAL

Haemoglobin values (range 4·3 to 11·4 g/dl) showed a weak negative correlation with age ($r = -0{\cdot}41$; $p < 0{\cdot}05$) and no significant sex difference. Reticulocyte counts (range 3·8% to 20·5%) showed no significant relation with age and sex.

RENAL STRUCTURE AND FUNCTION

Mean kidney length was 12·3 cm (range 10·1 to 14·8 cm), or 7·5% (range 6·3% to 9·2%) of standing height, and correlated with creatinine clearance when corrected for surface area ($r = 0{\cdot}61$; $p < 0{\cdot}001$). Morphological abnormalities included loss of caliceal cupping in nine patients and irregularities of the renal outline in five. One patient had a cystic extension from one calix, but no other features of papillary necrosis occurred and no patient had any features of lower urinary tract obstruction. Midstream urine cultures were sterile in all cases and no excess of pus cells was found.

Serum creatinine concentration exceeded the upper normal limit (124 μmol/l; 1·4 mg/100 ml) in three patients, and serum urea exceeded the upper normal limit (5·5 mmol/l; 33 mg/100 ml) in seven. Serum urea concentrations were higher than those of a group of 25 randomly selected patients with SS disease aged 18-39 years (geometric mean 5·5 *v* 2·9 mmol/l (33·1 *v* 17·5 mg/100 ml); $p < 0{\cdot}001$) but there was no significant difference in serum creatinine values.

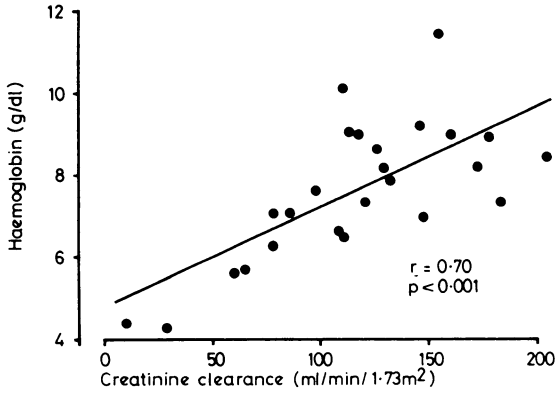

FIG 1—Relation between haemoglobin concentration and creatinine clearance.

Creatinine clearance varied widely (mean 116 ml/min/1·73 m²; range 11-204 ml/min/1·73 m²) and was below 80 ml/min/1·73 m² in six patients, who were considered on this basis to have renal insufficiency. In all six creatinine clearance was below the fifth percentile for age and sex in a normal population.[5] Comparison of these patients with the rest of the group failed to disclose differences in age, clinical features, blood pressure, symptoms of renal failure, or reticulocyte count, though differences were apparent in proteinuria, haemoglobin concentration, and findings on intravenous urography. Proteinuria greater than 100 mg/day was more common in renal insufficiency ($p = 0{\cdot}04$), but only one patient lost over 1 g/day. Haemoglobin values were significantly lower in the group with renal insufficiency (mean 5·6 ± SD 1·1 g/dl *v* 8·2 ± 1·2 g/dl; $p < 0{\cdot}001$), and there was a strong positive correlation between the haemoglobin concentration and creatinine clearance ($r = 0{\cdot}70$; $p < 0{\cdot}001$; fig 1), which was particularly striking in patients with creatinine clearance below 100 ml/min/1·73 m² ($r = 0{\cdot}96$; $p < 0{\cdot}001$). Renal insufficiency was significantly associated with irregularity of the renal outline in the intravenous urogram ($p = 0{\cdot}008$) but not with caliceal clubbing ($p = 0{\cdot}09$). Though ages of patients with and without renal insufficiency were not significantly different, there was a negative correlation between creatinine clearance and age in the entire group, but this was weak ($r = -0{\cdot}47$; $p < 0{\cdot}05$; fig 2).

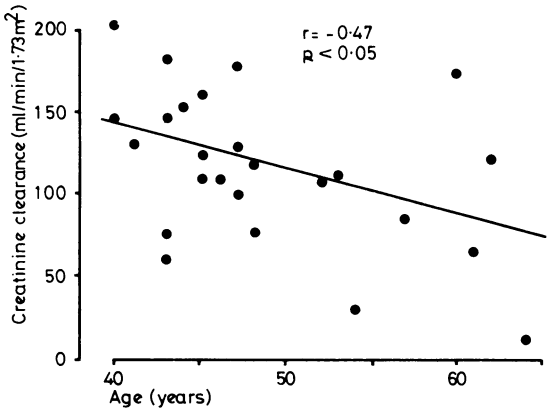

FIG 2—Relation between creatinine clearance and age.

Discussion

This study shows that high glomerular filtration rates, which are uniform in young patients with SS disease,[2] may persist into adult life in some patients but not in others. Contrary to the gradually falling glomerular filtration rate observed with age in the normal population,[5] there was only a weak negative correlation with age, and two patients over 60 had creatinine clearances of 120 ml/min/1·73 m² or more. On the other hand, six of the 25 unselected patients with SS disease had creatinine clearances below the expected fifth percentile for age and sex, supporting the suggestion that renal failure is an important factor in mortality.[4] The mechanism for this reduction in glomerular function is not clear. Younger adults with SS disease may be susceptible to the nephrotic syndrome complicated by uraemia,[6] but since none of our patients had been nephrotic or had heavy proteinuria it seems unlikely that the glomerular disorder associated with this syndrome[7] could have been responsible for renal insufficiency. Published work on the histological structure of the kidney in SS disease does not include patients of the age we studied, but we assume that if the interstitial and minor glomerular changes described in younger adults with normal glomerular function[8] became more pronounced reduction of glomerular function might result. Alternatively a third pattern of damage, cortical scarring, which has been recorded in sickle haemoglobin C disease,[9] might also produce renal failure. Necropsy in one patient in our study, who died in renal failure (creatinine clearance 28 ml/min/1·73 m²), showed small kidneys with areas of cortical atrophy surrounding islands of preserved parenchyma in a pattern corresponding to the irregularity of renal outline seen on intravenous urography. The association of this radiological abnormality with renal insufficiency and its tendency to be more common in older patients[10] suggest that this patchy process may be responsible for reduction of creatinine clearance. Whatever the process causing renal insufficiency it is clinically asymptomatic, without hypertension, associated with minor proteinuria, and generally signalled only by a falling haemoglobin concentration.

The correlation between haemoglobin value and creatinine clearance was striking. Anaemia alone is not associated with a significant reduction in glomerular filtration,[11] and it seems likely that renal insufficiency caused the falling haemoglobin concentration since this occurs in patients with SS disease and obstructive uropathy (unpublished observations) and in normal people with renal insufficiency. Anaemia in renal insufficiency in patients without SS disease, however, does not usually occur

until creatinine clearance[12] falls below 60 ml/min/1·73 m² or the serum urea concentration[13] exceeds 8·3 mmol/l (50 mg/100 ml), whereas haemoglobin concentrations fall in SS disease with higher clearances and occasionally normal urea values. One explanation for this difference would be that the greatly expanded erythron in SS disease is very dependent on erythropoietin and readily reflects reduced production associated with mild renal disease.

The results show that a fall in steady-state haemoglobin concentration is a sensitive and early indicator of renal impairment. The high prevalance of renal insufficiency in older patients with SS disease suggests that renal function and haemoglobin values should be monitored carefully.

Requests for reprints should be sent to Dr A G Morgan.

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Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes

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Abstract

A new, non-invasive method of measuring pulmonary epithelial damage in man was compared with traditional tests of small-airway function. Pulmonary epithelial permeability was expressed as the half-time clearance from the lung into blood of ^{99m}Tc-diethylene triamine-penta-acetic acid (^{99m}Tc-DTPA) deposited predominantly in the alveoli from an inhaled aerosol.

Recovery from abnormal pulmonary permeability was recorded after stopping smoking for 21 days in a group of young symptomless cigarette smokers. Before stopping smoking there was a significant correlation between half-time lung clearance of ^{99m}Tc-DTPA and carboxyhaemoglobin concentration ($r=0·69$; $p<0·05$). There was no correlation between carboxyhaemoglobin value and closing volume, the only other abnormal test of airway function. Twenty-four hours after stopping smoking the mean half-time lung clearance of ^{99m}Tc-DTPA had increased significantly ($p<0·001$) from a baseline of 15·8 min (SEM 1·3 min) to 25·5 min (SEM 2·5 min). The mean half-time clearance continued to increase to a maximum of 35·5 min (SEM 3·1 min) at seven days, but was significantly less than the reported half-time clearance for non-smokers (59 min, SEM 5 min). There was no significant change in half-time clearance in six subjects who continued to smoke over a similar period. For individuals the greater the permeability the smaller was the recovery in the non-smoking period. There were no significant changes in results of any other tests of small-airway function.

This index of pulmonary permeability is a very sensitive test of damage to lung epithelium caused by smoking. It shows both severity and recovery of function, which are not detectable by conventional tests.

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Introduction

We recently described a new test of pulmonary function which is used to derive an index of altered permeability of the pulmonary epithelium to the chelate ^{99m}Tc-diethylene triamine-penta-acetic acid (^{99m}Tc-DTPA).[1] We assumed that the permeability of the walls of small airways and alveoli is the major determinant of this index because an aerosol of ^{99m}Tc-DTPA, particle size 1 μm, will deposit predominantly in the alveolated airways.[2 3] During the development of this technique we noticed that a group of symptomless cigarette smokers had a significantly greater permeability than non-smokers. One of these subjects with increased permeability gave up smoking and we observed a reduction of the permeability defect.[1] We designed the present study to investigate in more detail the relation between cigarette smoking and pulmonary epithelial permeability, and to examine the time course and degree of reduction in permeability after stopping cigarette smoking. We compared the changes in permeability after stopping smoking with the results of sequential measurements of small-airway function using traditional tests and a new test developed in our laboratory.[4]