Rapidly progressive glomerulonephritis in Black children

A report of 4 cases

M. G. DILIMA, M. ADHIKARI, H. M. COOVADIA

Summary

Rapidly progressive glomerulonephritis in children is rare, and we have therefore described 4 cases in Black children. All had evidence of a preceding streptococcal infection and there were crescents in more than 80% of the glomeruli seen on histological examination. The dominant clinical features were oliguria or anuria in a setting of nephritis or nephrotic syndrome, with a relentless progression to chronic renal failure and death. Quadruple therapy with cyclophosphamide, steroids, heparin and dipyridamole in 3 of the patients was of no lasting benefit and was attended by severe complications. Guidelines to the monitoring of children with post-streptococcal glomerulonephritis for the early detection of this uncommon complication are given.

Rapidly progressive glomerulonephritis (RPGN) is uncommon in adults and even rarer in children. A current review of the disease in American children is based on 1 in 2,300,000 children with post-streptococcal glomerulonephritis (PSGN) is one of the commonest renal diseases in Black children admitted to hospital and is recognized as an antecedent event in the development of RPGN. The syndrome of RPGN, however, has not been adequately described in Black children; in fact, in a recent symposium on renal disease in the tropics the disease was not mentioned. We therefore describe our experience with 4 patients who were diagnosed as having RPGN. Details of the patients and their treatment are summarized in Tables I and II.

Case reports

Case 1

A 9-year-old Black boy was transferred from a peripheral hospital where he had been treated for acute glomerulonephritis. The duration of the illness was unknown. A history of previous hospitalization or a relevant family history was not available.

On admission he had evidence of healing impetigo, enlarged kidneys were demonstrated on ultrasonography. The initial urea and electrolyte levels, determined on admission, were as follows: blood urea 58 mmol/l, serum sodium 122 mmol/l, serum potassium 8,4 mmol/l, serum chloride 96 mmol/l and plasma bicarbonate 15 mmol/l. Peritoneal dialysis was therefore commenced, the blood urea level decreased to 15,2 mmol/l, and the serum sodium, potassium and chloride and plasma bicarbonate levels returned to normal. Subsequently the urea level stabilized at 30 mmol/l. The patient remained anuric for 3 weeks and oliguric until death. Examination of the first available specimen of urine revealed albumin 3+, subsequent examinations of the urine being non-contributory. In particular there were no cells or casts.

The serum osmolality was 329 mOsm/kg and the urine osmolality 313 mOsm/kg. The glomerular filtration rate was not measured. The serum creatinine level was 675 mmol/l. Serum protein electrophoresis revealed an albumin level of 24,4 g/l and the following globulin levels: α-globulin 2,5 g/l, α₁-globulin 9,3 g/l, β-globulin 15,6 g/l and γ-globulin 15,2 g/l. The serum cholesterol level was 4,27 mmol/l. The streptozyme test was positive; the antistreptolysin O titres were 100 U/ml on admission and the test became negative after 10 days. The C-reactive protein test was positive on admission and when performed subsequently. Chest radiographs taken on admission and after 10 days revealed lamellar effusions at the base of both lungs. Enlarged kidneys were demonstrated on ultrasonography.

Antinuclear factor, parietal cell, smooth-muscle and mitochondrial antibodies were absent, and hepatitis B surface antigen (HBsAg) was not detected in the serum. Initially the C3 level was 0,04 g/l (normal 0,90 ± 0,19 g/l (mean ± SD)) and the C4 level 0,72 g/l (normal 0,47 ± 0,18 g/l (mean ± SD)). Seven days later the C3 level had risen to 0,98 g/l and the C4 level to 0,90 g/l. The haemoglobin concentration was 11,1 g/dl and the white cell count 36,9 x 10^9/l with 94% neutrophils, 4% lymphocytes and 2% monocytes. The factor VIII procoagulant activity was 156% (normal range 50-150%). Salmonella typhi was cultured from the blood after the patient had been in hospital for 2 weeks. The Widal reaction and examination of stool and urine specimens for S. typhi were negative on several occasions. A repeat blood culture after 17 days of treatment with amoxycillin was negative. Two weeks later Shigella flexneri was cultured from the stools. The bilharzia complement-fixation test (CFT) was negative, and the liver enzyme values were within normal limits. The blood pressure was elevated 1 day after admission and stabilized at 150/100 mmHg despite antihypertensive therapy. The patient had persistent generalized oedema throughout the period of hospitalization and became progressively anaemic. At a haemoglobin concentration of 6,3 g/dl, packed cells and 20% albumin and frusemide were administered slowly in order to correct the anaemia and attempt to induce a diuresis. The patient died 20 hours later, having been in hospital for 6 weeks and after treatment with diuretics and antihypertensives together with routine care.

Histological examination of renal tissue at autopsy confirmed the diagnosis of RPGN, more than 80% of the glomeruli showing crescents. The probable cause of death appeared to have been terminal heart failure with left ventricular hypertrophy.

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TABLE I. CLINICAL FEATURES

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Peak BP (mmHg)</th>
<th>Haematuria</th>
<th>Proteinuria</th>
<th>Oliguria or anuria</th>
<th>Skin lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>M</td>
<td>150/100</td>
<td>Nil</td>
<td>3+</td>
<td>Yes</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>M</td>
<td>140/100</td>
<td>Microscopic</td>
<td>3+</td>
<td>Yes</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>F</td>
<td>150/100</td>
<td>Nil</td>
<td>+</td>
<td>Yes</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>F</td>
<td>180/140</td>
<td>Macroscopic</td>
<td>2+</td>
<td>Yes</td>
<td>Absent</td>
</tr>
</tbody>
</table>

BP = blood pressure.

TABLE II. INVESTIGATIONS AND OUTCOME

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Blood urea (mmol/l)</th>
<th>Serum creatinine (mmol/l)</th>
<th>ASOT/ST</th>
<th>C3 (g/l)</th>
<th>Factor VIII (%)</th>
<th>Crescents in glomeruli</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>675</td>
<td>Positive</td>
<td>0.04</td>
<td>156</td>
<td>80</td>
<td>Supportive</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>155</td>
<td>Positive</td>
<td>0.68</td>
<td>182</td>
<td>100</td>
<td>QCD</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>580</td>
<td>Positive</td>
<td>0.12</td>
<td>180</td>
<td>80</td>
<td>QCD</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>508</td>
<td>Positive</td>
<td>0.70</td>
<td>201</td>
<td>100</td>
<td>QCD</td>
<td>Died</td>
</tr>
</tbody>
</table>

ASOT/ST = antistreptolysin O titre/streptolysin test; QCD = quadruple chemotherapy.

Case 2

An 11-year-old Black boy was transferred to the King Edward VIII Hospital, Durban, from a peripheral hospital with a 2-day history of generalized oedema. He had been admitted to that hospital 7 months earlier with acute glomerulonephritis which had responded well to penicillin, frusemide, hydralazine, and protein restriction. There was no relevant family history.

On admission he had generalized oedema, gross ascites and a blood pressure of 100/70 mmHg. The rest of the systemic examination was negative. He was anuric for 3 days and thereafter became oliguric. Examination of the urine revealed 30 leucocytes per high-power field (HPF) and red blood cells 30/HPF with hyaline and granular casts. Serum protein electrophoresis revealed an albumin level of 12.4 g/l and the following globulin levels: α1-globulin 1.4 g/dl, α2-globulin 14.1 g/l, β-globulin 5.9 g/l and γ-globulin 10.2 g/l. The total protein level was 44.0 g/l and the serum cholesterol level 11.61 mmol/l. The serum and urine osmolality were 308 mOsm/kg and 385 mOsm/kg respectively.

The blood urea level on admission was 19.0 mmol/l, the serum creatinine level 155 mmol/l and the glomerular filtration rate 17 ml/min. Serum sodium, potassium and chloride and plasma bicarbonate levels were within normal limits. One month later the blood urea level had risen to 35.0 mmol/l and the patient developed persistent generalized oedema with evidence of fluid overload. Peritoneal dialysis was performed. Over a period of 3 weeks the blood urea level increased gradually but steadily to 35.4 mmol/l and fluid overload developed once more. A second peritoneal dialysis was carried out, followed by a renal biopsy.

The streptozyme test was positive initially and became negative after 2 months. The antistreptolysin O titre on admission was negative. The C-reactive protein test was positive and the Wassermann and Widal reactions negative. Antinuclear factor, parietal cell, mitochondrial and smooth-muscle antibodies and HBSAg were not detected in the serum. The bilarhia CFT was positive. Biopsy of the rectal mucosa did not reveal bilarhia. The haemoglobin concentration was 8.3 g/dl and the white cell count 13,1 x 10^9/l with 66% neutrophils, 24% lymphocytes, 5% monocytes, 4% eosinophils and 1% basophils. The patient had been transfused with packed cells before renal biopsy. The factor VIII procoagulant activity was 182%.

The complement levels on admission and 2 months later respectively were as follows: C3 — 0.68 g/l and 0.58 g/l; C4 — 0.60 g/l and 0.68 g/l; factor B — 0.22 g/l and 0.14 g/l (normal 0.34 ± 14 g/l). A chest radiograph on admission was normal. Ultrasonography on admission revealed the kidneys to be normal in size, but progressive enlargement had taken place 6 weeks later. Renal biopsy showed rapidly progressive (crescentic) glomerulonephritis. Not one of 13 glomeruli was normal. Nine glomeruli showed extensive sclerosis and in some of these residual crescents were detectable. IgA deposits were present along the basement membrane of some tubules but no glomeruli were present for immunofluorescent examination. During the patient’s stay in hospital he remained oliguric or anuric, had persistent generalized oedema and became hypertensive after an initial period during which his blood pressure had been normal. He received antihypertensive drugs, diuretics and quadruple chemotherapy, i.e. heparin, dipyridamole, cyclophosphamide and prednisone. Ten days after starting quadruple therapy he developed a pericardial friction rub. The cardiac shadow was enlarged, and the lung fields congested; a chest radiograph at this stage showed a small right-sided pleural effusion. Ultrasonography showed cardiomegaly with no pericardial effusion. The quadruple chemotherapy was therefore stopped. The patient died after 3 months in hospital.

Case 3

A 4-year-old Black girl was admitted with a 3-day history of puffiness of the face. There was no relevant past or family history of illness. On examination she had oedema of the legs and face, healing impetigo on the lower limbs and a blood pressure of 150/100 mmHg. There was no evidence of fluid overload. The rest of the systemic examination was negative. Throughout her first 2-month stay in hospital she remained oliguric or anuric, hypertensive, oedematous and uraemic. Peritoneal dialysis was carried out on 3 occasions and renal biopsy was performed after the last dialysis.

Examination of the first available urine specimen was negative, and in particular there were no cells or protein. Subsequent urine samples revealed at most protein 1+. Klebsiella pneumoniae was cultured from the urine on 3 occasions. On admission the blood urea level was 33.1 mmol/l and the serum creatinine level 580 mmol/l. Serum sodium and potassium and plasma bicarbonate levels were normal. The total serum protein level was 62 g/l with albumin 27 g/l and globulin 35 g/l. The streptozyme test was positive but the antistreptolysin...
O titre was negative. The C-reactive protein test was positive. Antinuclear factor, parietal cell, mitochondrial and smooth-muscle antibodies and HBsAG were not detected in the serum. The Wassermann and Widal reactions were negative. The bilharzia CFT was positive.

The haemoglobin concentration was 10.3 g/dl and the white cell count 12.5 x 10^9/l with 61% neutrophils, 33% lymphocytes, 2% monocytes, 1% eosinophils and 1% basophils. Factor VIII procoagulant activity was 180%. Blood cultures were negative. The serum and urine osmolality were 285 mOsm/kg and 195 mOsm/kg respectively. The patient was given antihypertensive drugs, diuretics and quadruple chemotherapy and transfused when necessary. While on the quadruple chemotherapy she developed bilateral bronchopneumonia and a pericardial friction rub. The initial chest radiograph was normal but chest radiographs taken after the quadruple chemotherapy showed infective changes in both lung fields. Ultrasonography showed bilateral enlargement of the kidneys, and after the development of the pericardial friction rub there was seen to be cardiac enlargement with no evidence of pericardial effusion.

After 2 months the patient was signed out of hospital by her parents. She was subsequently admitted a second time for 14 days with a urinary tract infection which was treated successfully. The blood pressure and blood urea levels were normal.

Within a week after the second discharge the patient was admitted for the third time with features suggestive of chronic renal failure and congestive cardiac failure. She was hypertensive, oedematous and uraemic, and had a systolic murmur at the apex, probably secondary to the cardiomegaly which had followed the elevated blood pressure. There was no evidence of rheumatic heart disease. The patient is alive and is being treated for chronic renal failure.

Case 4

An 8-year-old Black girl was transferred from a peripheral hospital where she had been treated for acute glomerulonephritis with hypertension. She had been ill for 3 months. There was no relevant past or family history of illness.

On examination she had generalized oedema, a blood pressure of 160/110 mmHg, oliguria and macroscopic haematuria. There was no evidence of fluid overload. The rest of the systemic examination was negative.

Examination of the urine revealed leucocytes 80/HPF, red blood cells 800/HPF and proteinuria 2+. Urine culture revealed no organisms. The total protein in a 24-hour specimen of urine was 6.32 g. The patient remained oliguric until death, except for 10 days of diuresis immediately after the initiation of quadruple chemotherapy.

The blood urea level on admission was 24.6 mmol/l and the serum creatinine level 508 mmol/l. Serum sodium, potassium and chloride and plasma bicarbonate levels were within normal limits. Ten days after admission the blood urea level had increased to 26.1 mmol/l and the oedema had increased despite adequate doses of diuretics. Peritoneal dialysis was performed, followed by renal biopsy. Serum protein estimation showed a total protein level of 56 g/l with albumin 24 g/l and globulin 32 g/l. The serum cholesterol level was 5.08 mmol/l. The serum and urine osmolality were 310 mOsm/kg and 257 mOsm/kg respectively.

The streptozyme test was positive but the antistreptolysin O titre was negative; the C-reactive protein test was positive and the Widal reaction negative. Initially the haemoglobin concentration was 8.2 g/dl and the white cell count 13.2 x 10^9/l with 65% neutrophils, 20% lymphocytes and more than 12% eosinophils. The platelet count was normal.

Parasites were not detected on examination of stool and urine specimens. The patient received packed-cell transfusions on 2 occasions because of a falling haemoglobin concentration. The factor VIII procoagulant activity was 180%.

The complement levels on admission and a month later respectively were as follows: C3 - 0.70 g/l and 0.64 g/l; C4 - 0.44 g/l and 0.40 g/l; factor B - 0.68 g/l and 0.32 g/l. Chest radiographs on admission and subsequently showed features compatible with acute glomerulonephritis.

Renal biopsy confirmed the diagnosis of RPGN. All the 10 glomeruli seen showed crescents. IgM granular deposits were seen along the basement membrane of the glomeruli on immunofluorescent examination.

The patient was given antihypertensive drugs, diuretics and quadruple chemotherapy, together with routine care. She was drowsy and acidotic 1 day before her death, after having been in the ward for 11 weeks. Autopsy revealed large pale kidneys which on light microscopy showed fibrosis and sclerosis of all glomeruli with progressive tubular atrophy and interstitial fibrosis.

Discussion

This report describes the features of RPGN in 4 Black children who were all seen within a period of 1 year. This temporal aggregation of cases of an extremely rare disease is not easily explained. It is possible that some combination of circumstances enhanced the pathogenicity of a particular subtype of streptococcus, resulting in severe renal disease. In most series about one-third of cases of RPGN in adults are associated with systemic vasculitis syndromes, and a minority follow infections. Only 1.6% are related to antecedent streptococcal glomerulonephritis. However, in 2 series of children with RPGN PSGN was the antecedent event in 32% and 63% respectively. The 4 children reported here did not have evidence of systemic vasculitis syndromes, which are in any case infrequent in our patients. PSGN is extremely common in Black children admitted to the King Edward VIII Hospital, and evidence for a post-streptococcal aetiology in our patients was the combination of healing impetigo (in 2 patients), positive streptozyme tests and diminished C3 levels. On the basis of their results, Cunningham et al. speculated that RPGN may follow pharyngeal and not skin streptococcal infection. Our data do not support this. RPGN is said to be an extremely rare complication of acute post-streptococcal glomerulonephritis, the incidence being <1%. We admit approximately 250 patients with PSGN every year, and the 4 cases of RPGN reported are the first we have seen. Our experience therefore accords with that of other units.

In case 1 the second blood culture (after 11 days of hospitalization) isolated S. typhi. However, the clinical features did not resemble the typical picture of typhoid glomerulonephritis and we therefore believe that the patient was cross-infected in the ward.

The clinical manifestations in crescentic glomerulonephritis are usually variable, including oliguria or anuria, nephritis, proteinuria or the nephrotic syndrome. The 4 cases reported here illustrate these typical presentations, all the children having been oliguric or anuric, 3 having nephritis and 2 demonstrating features of the nephrotic syndrome. In Durban more than 90% of Black children with PSGN will recover clinically (i.e. from hypertension, oedema and oliguria) by the 2nd week in hospital. We must therefore consider renal biopsy to establish the diagnosis of RPGN in the case of any child with PSGN who does not recover within this period. There has been a suggestion, not entirely supported by our data, that clinical pointers to a
diagnosis of RPGN in children with PSGN are anaemia, marked uraemia and hypergammaglobulinaemia. Increased levels of factor VIII procoagulant activity can be used as an index of the extent of immunopathological injury to the glomerular capillaries. This can be a help in assessing the severity of renal disease. In all our 4 patients with RPGN the factor VIII levels were increased beyond those found in children with PSGN, who generally do well.

The outcome is thought to be better in RPGN following streptococcal infections. The study by Cunningham et al. and our data do not support this. As suggested by Cunningham et al. the prognosis of RPGN does not depend on the aetiology but on the extent of renal damage as reflected in the number of glomeruli with crescent formation.

Renal biopsy proved all 4 of our patients to have had severe RPGN, with more than 80% of glomeruli involved. This denotes a poor prognosis, as pointed out by Kincad-Smith. If over 50% of the glomeruli in an adequate sample show crescents spontaneous recovery is rare, while if more than 80% of the glomeruli show crescents recovery does not occur. Our patients all had a protracted course and poor outcome.

The outcome in untreated RPGN is known to be very poor, death occurring within weeks to months from the time of presentation. Anticoagulant therapy has been known to have a striking effect on the renal lesions in experimental nephritides and to produce immediate clinical improvement in some clinical trials. Quadruple therapy was tried in 3 of our 4 patients, but in 2 the expected improvement in renal function did not occur and it was transient (10 days) in 1 (case 4). In this patient the histological changes showed marked progression to glomerular sclerosis and fibrosis and interstitial fibrosis. The complications of therapy were life-threatening. Two patients developed pericarditis with the appearance of a pericardial friction rub while on quadruple therapy. Although pericardial fluid was not demonstrated on ultrasonography, however, suggesting a fibrous pericarditis. Uraemia could have caused the pericarditis. Haemorrhagic complications have been associated with anticoagulant therapy in 2 studies. Haemorrhagic pericarditis should therefore be considered a possibility in our 2 patients, 1 of whom also developed severe bilateral bronchopneumonia while on quadruple therapy. Although previous studies have demonstrated benefit from quadruple therapy, in our patients this treatment was attended by grave hazards which required discontinuation of the drugs. In Cunningham et al.’s series 2 patients with prolonged oliguria did not respond to anticoagulant therapy. All 4 of our patients had prolonged oliguria or anuria, and this may account for their failure to respond to anticoagulant therapy.

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REFERENCES

News and Comment/Nuus en Kommentaar

Kriochirurgiese behandeling van karsinoom in situ van die cervix uteri

Kriochirurgie bestaan uit die applikasie van sterk verkoelde instrumente wat die lokale vernietiging van weefsel veroorsaak. ’n Temperatuur van ten minste -40° sal byna altyd nekrose van instrumente wat die lokale vernietiging van weefsel veroorsaak, wennings die lokale vernietiging van weefsel veroorsaak. Kriochirurgie bestaan uit die applikasie van sterk verkoelde instrumente wat die lokale vernietiging van weefsel veroorsaak.

Kriochirurgiese behandeling van karsinoom in situ van die cervix uteri is een van die meeste effektiewe behandeling van karsinoom. Monobactams are a family of monocyclic β-lactam antibiotics produced by bacteria. They are markedly different from penicillins and cephalosporins, which are bicyclic β-lactam antibiotics originally detected in fungi.

SQ 26776, the first totally synthetic monobactam, has very significant antimicrobial activity and appears to be specifically directed against Gram-negative bacteria, particularly those causing infections in hospital patients undergoing complicated medical and surgical procedures. Most Gram-negative organisms that can de-activate penicillins and many cephalosporins are unable to destroy the much more stable monobactam.

Human volunteer studies to test the new drug are already in progress and clinical trials are pending.

Monobactams

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