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Rapidly Progressive Glomerulonephritis in Children: An Analysis of 18 cases

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Summary

Abdurrahman MB, Narayana PT and Babaoye FA. Rapidly Progressive Glomerulonephritis in Children: An Analysis of 18 cases. *Nigerian Journal of Paediatrics* **1982; 9: 55.** The clinical course as well as the renal pathology in 18 children with rapidly progressive glomerulonephritis is described. The disease was characterised by prolonged oliguria, generalised oedema, hypertension, hypoalbuminaemia and anaemia. Fifty-four per cent of the patients tested had hepatitis-B surface antigenaemia. Deposition of immunoglobulins and complement occurred in the glomeruli of all the six kidney biopsies tested. The prognosis was poor, with 39% mortality. There were two defaulters and nine patients are alive. Of the nine living patients, seven have developed features of chronic renal disease.

Introduction

ALTHOUGH the prognosis in children with acute glomerulonephritis (AGN) is generally good,[1 2] there is a small group of children with an unusual form of the disease characterised by rapid progression to renal failure in weeks or months. This unusual form is associated with extensive proliferation of extracapillary cells to form crescents surrounding most glomeruli. This entity is variably termed rapidly progressive glomerulonephritis (RPGN), extracapillary glomerulonephritis, subacute glomerulonephritis or crescentic glomerulonephritis. Acute glomerulonephritis is relatively common in Zaria, with an average of 40 cases seen in children yearly (unpublished data). The purpose of the present communication is to present our experience with RPGN in children, particularly its clinical and laboratory features which distinguish this group of children from those with AGN.

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Patients and Methods

A retrospective analysis was carried out on all children with RPGN admitted to the Ahmadu Bello University Hospital (ABUH), Zaria, from January 1976 to December 1980, a period of five years. The criteria for inclusion in the study were (1) acute hypertension, oliguria and azotaemia, (2) a renal biopsy specimen containing not less than ten glomeruli, of which at least, 25% showed crescent formation. Hypertension was defined as a blood pressure greater than 120/80

mmHg in children less than 10 years old and greater than 140/90 *mmHg* in children ten years old and above. Oliguria was defined as a 24-hour urine output less than 20 ml/kg body weight.

The data extracted from the patients' case-folders included the clinical features, management, course and outcome. For comparison, the same data were extracted from the case-folders of patients with AGN. Standard laboratory methods were used to carry out the investigations which included haemoglobin (Hb), haemoglobin genotype, urinalysis, culture of urine, skin or throat as indicated, serum urea, creatinine, electrolytes, complement C3, proteins and anti-streptolysin O titre (ASOT). Hepatitis-B surface antigenaemia (Hbs-Ag) was determined by counter-current immunoelectrophoresis. Percutaneous kidney biopsy was performed in each patient and the biopsy specimen for light microscopy was fixed in 10% formol saline. Sections were cut and stained with two or more of the following: haematoxylin and eosin, periodic acid-Schiff, Masson trichrome and methenamine silver. For immunofluorescence, the tissues were snap-frozen with carbon dioxide and the sections cut and stained with commercial monospecific antisera to human immunoglobulins G, A and M, complement C3 and hepatitis-B surface antigen.

Results

There were 18 children (10 males and 8 females), aged between 4 and 15 years (mean, 7 years), who satisfied the above criteria. The patients were divided into two groups, namely: those with evidence of streptococcal infection (10 cases) and those without (8 cases). Evidence of streptococcal infection was based on a combination of infected scabies lesions, isolation of group A *B-haemolytic streptococcus* from the skin lesion, low serum complement, raised ASOT and endocapillary proliferation in kidney biopsy. The features in the 18 patients are shown in Tables I and II (a and b).

TABLE I

Age, Sex and Blood Pressure in 18 Children with Rapidly Progressive Glomerulonephritis

	Age (Yrs)	*Sex*	*Blood Pressure (mm Hg)*
Group I			
1	4	M	100/60
2	10	F	150/105
3	13	F	170/110
4	7	M	100/75
5	8	F	140/100
6	9	F	160/130
7	5	F	150/110
8	7	M	140/100
9	8	M	140/100
10	10	M	170/120
Group II			
11	6	F	100/60
12	5	M	90/60
13	6	M	125/86
14	7	M	130/90
15	15	M	130/80
16	3	F	90/70
17	8	M	170/110
18	5	F	140/90

Group I Consisted of patients with evidence of streptococcal infection.

Group II Consisted of patients without evidence of streptococcal infection.

Clinical Features

All the patients had oedema, generalized in 16 and localized to the face and feet in two cases. The admission diagnosis was nephrotic syndroma in nine cases. There was a history of haematuria in six cases, skin rashes or infection in five, oligurie

TABLE II(*a*)

Laboratory Data, Treatment and Outcome in 10 Children with Rapidly Progressive Glomerulonephritis (Group I)

	Serum			*C3* (% *of normal*)	*Hb* (*g/dl*)	*ASOT* (*Todd units*)	*Serum HBsAg*	*Treatment*	*Outcome*
	albumin (*g/l*)	*urea* (*mmol/l*)	*creatinine* (*umol/l*)						
1	20	6.2	120	27	5.8	320	negative	C	Unknown
2	28	6.7	64	123	8.8	80	negative	C	Alive
3	32	34.3	87	72	7.2	20	ND	C	Died
4	15	11.5	63	78	10.7	20	+	H	Alive
5	23	19.4	265	80	8.4	20	+	Pred	Died
6	21	6.7	138	40	6.7	320	negative	C	Unknown
7	26	10.6	93	50	9.4	80	+	PD+H	Alive
8	23	22.8	208	64	3.2	80	+	C	Died
9	26	21.0	1012	81	4.4	80	negative	Pred	Died
10	27	22.0	486	60	8.6	40	ND	C	Alive

TABLE II(*b*)

Laboratory Data, Treatment and Outcome in 8 Children with Rapidly Progressive Glomerulonephritis (Group II)

	Serum			*C3* (% *of normal*)	*Hb* (*g/dl*)	*ASOT* (*Todd units*)	*Serum HBsAg*	*Treatment*	*Outcome*
	albumin (*g/l*)	*urea* (*mmol/l*)	*creatinine* (*umol/l*)						
11	28	7.0	48	95	10.7	40	+	C	Alive
12	13	4.0	40	119	9.9	40	negative	H	Alive
13	22	24.0	200	151	6.2	20	ND	PD	Alive
14	24	24.5	189	64	3.2	80	+	PD	Died
15	35	54.0	1204	90	5.4	40	ND	Nephrectomy	Died
16	18	4.1	90	124	11.5	20	+	Cyclo+Pred	Alive
17	18	21.5	212	101	8	80	negative	C	Died
18	25	25.0	25	100	9.7	20	ND	C	Alive

C = Conservative
Cyclo = Cyclophosphamide
H = Heparin
ND = Not done
PD = Peritoneal dialysis
Pred = Prednisolone

in three, and dyspnoea in two. The mean duration of oligo-anuria was 12 days (range, 5–23 days) compared with four days (range, 2–8 days) in patients with AGN. Twelve (66.7%) of the 18 patients had hypertension, while there was evidence of circulatory overload or cardiac failure in five cases, two of whom had hypertension. Five children had infected scabies. There was no case of pharyngitis. Hypertension was more frequent in children with streptococcal infection.

The patients with RPGN differed from those with AGN only in having more severe and prolonged oliguria.

Investigations

The urine contained variable amounts of protein, blood and red cell casts. Pathogens were cultured from the urine of four children. Haemolytic streptococci were cultured from infected scabies skin lesions in three out of five patients. Complement C3 level was less than 70% of normal in six patients. Serum proteins, particularly albumin (range, 13–35 g/l), were low. ASOT was slightly elevated in two patients who also had low serum C3, but minimal endocapillary proliferation of the glomeruli. The mean Hb level was 7.7g/dl compared with 10.2 g/dl in patients with AGN. There was severe anaemia (Hb < 5 g/dl) in four cases and moderate (Hb 5–9 g/dl) in 11 others. There was no case of haemoglobin genotype SS. Apart from haematuria, there was no other obvious source of blood loss, or any evidence of haemolysis. HBs Ag was detected in the sera of seven out of 13 patients. Compared to children with AGN, those with RPGN had increased frequency and severity of anaemia and low serum albumin. However, there was no significant difference in the laboratory findings between the streptococcal and non-streptococcal RPGN.

Renal biopsy was carried out within four weeks of onset of symptoms in all the patients except one whose biopsy was three months after. In addition to crescent formation (Fig. 1), eight

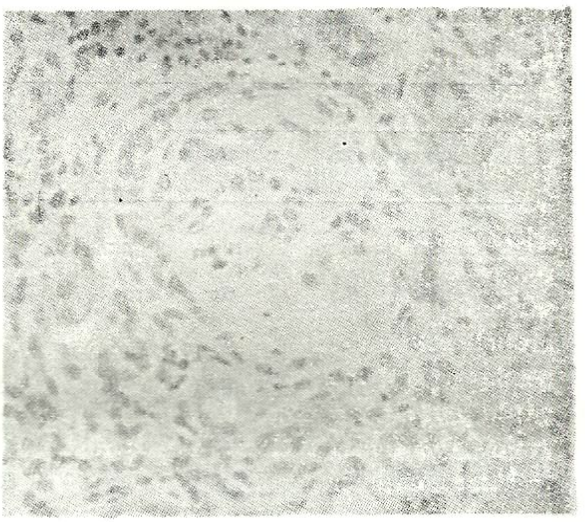

Fig 1 A photo-micrograph of kidney biopsy in rapidly progressive glomerulonephritis showing crescent formation.

biopsies showed endocapillary cell proliferation compatible with post-streptococcal AGN. In six biopsies, there was no endocapillary proliferation, while the remaining four showed prominent sclerosis (Fig. 2). The histopathological features in the five patients with infected scabies were compatible with post-streptococcal AGN. Addition of the two patients with elevated ASOT and low C3 to the eight with histologic features of post-streptococcal AGN, brought the total number of children with post-streptococcal RPGN to ten. Immunofluorescence was performed in

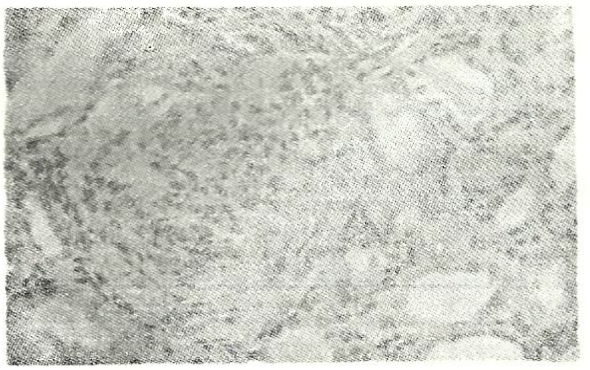

Fig 2. A photo-micrograph of kidney biopsy in advanced stage of rapidly progressive glomerulonephritis showing sclerosi

six cases. In five of these, there was granular deposition of IgG and C3 along the glomerular basement membrane. Two of the five cases also showed IgM and HBsAg fluorescence. There was a linear pattern of IgG, IgM and C3 in one biopsy.

Course, management and outcome

The hospital course was characterised by variable prolonged oliguria, deteriorating renal function and rising blood pressure. The duration of hospitalization ranging from 7 to 55 days (mean, 23 days) was longer than the mean of 10 days for children with AGN. All the patients were treated as acute renal failure with fluid restriction. Two patients had peritoneal dialysis alone, while a third patient had peritoneal dialysis and heparin. One of the two patients died, while the other survived but has progressively deteriorating renal function. The patient who had peritoneal dialysis and heparin is alive with normal renal function. Two patients, treated with heparin alone are alive, one with normal renal function and the other with persistent proteinuria. The two patients treated with prednisolone died, one from pneumonia and the other from renal failure. One child treated initially with prednisolone and subsequently with prednisolone and cyclophosphamide showed no response. This patient has persistent proteinuria and hypertension and a repeat renal biopsy showed advanced sclerosis and hyalinization. One 15-year old boy presented a year earlier with nephrotic syndrome. He presented acutely with oliguria, hypertension and severe haematuria. His intravenous pyelogram showed a filling defect in the left pelvis, with some amputation of the upper pole calyx proximally. He became progressively worse, as a result of which a left nephrectomy was carried out. The kidney showed foetal lobulation. Histologically, there was extensive crescent formation and sclerosis.

There were seven deaths, all occurring within four months of presentation. Four of the ten patients with streptococcal and three of the eight with non-streptococcal RPGN, died. Of the remaining eleven patients, two subsequently defaulted from the follow-up clinic, two have normal renal function tests, and seven have variable clinical and laboratory features of chronic renal failure.

Discussion

A comparison of RPGN cases reported from different centres is made difficult by lack of uniform definition. While some workers include RPGN secondary to systemic diseases with renal involvement such as in systemic lupus erythematosus,[3] others exclude such cases.[4] Some authors do not even consider post-streptococcal RPGN as being strictly RPGN.[5] Although crescent formation is accepted as the hallmark of RPGN, there appears to be no uniformity in the minimum percentage of affected glomeruli compatible with a diagnosis of RPGN. For instance, the minimum percentage used by Anand *et al*[4] was 25%, by Faarup *et al*,[6] 50% and by Brown *et al*[3] 60%. In the present study, 25% glomerular involvement was used as the criterion for the diagnosis of RPGN. The lack of uniform definition and criteria for the diagnosis of RPGN indicates that RPGN is not a single disease entity. It appears that RPGN is a syndrome caused by a variety of diseases with different pathogenesis but a common clinicopathological presentation. Moreover, the distinction between severe cases of AGN and RPGN is often difficult because the clinical presentation and histology of AGN may be similar to those of RPGN.[5]

The outstanding features in the present study were severe, generalized oedema and a high frequency of hypertension, anaemia and hypoalbuminemia. The oedema was so gross and the serum albumin so low that an initial diagnosis of nephrotic syndrome was made in nine patients. It is difficult to explain two findings in the present study, namely: a higher frequency of anaemia

in RPGN compared with AGN, and of hypertension in post-streptococcal RPGN than in non-streptococcal RPGN. Although the presence of fibrin in the glomeruli[7] suggests a possible derangement of the clotting system, the fibrin deposition was not occlusive. Moreover, there was no difference in the severity of haematuria between RPGN and AGN patients. Hepatitis-B surface antigenaemia was found in 54% in the present series. Hepatitis-B surface antigenaemia is not peculiar to RPGN since increased prevalence of the antigen has been observed in patients with other types of renal disease[8 9] and there is now ample evidence that HBsAg is nephropathic.[9 10]

Immunofluorescent studies showed deposition of immunoglobulins and C3 in all the six biopsies tested. In five biopsies, the deposit was granular, indicating antiglomerular basement membrane-mediated nephropathy. In a study of seven adult patients with RPGN, Lewis *et al*[7] found a linear pattern of deposition of immunoglobulins in six cases and a granular pattern in one. In contrast, Cunningham *et al*[11] reported granular IgG and C3 immunofluorescence in all the biopsies of nine children with RPGN. There are also reports of RPGN without deposition of immunoglobulins or C3.[5] These differences in the pattern of immunofluorescence reflect the multifactorial aetiology and pathogenesis of RPGN.

In the present series, the prognosis in RPGN of streptococcal aetiology, was not better than that of non-streptococcal RPGN, with a mortality of 40% and 38% respectively. A similar prognosis between the two types of RPGN has also been reported by Cunningham *et al*.[11] In contrast, Anand *et al*[4] and Leonard *et al*[12] reported better prognosis in children with streptococcal RPGN. The reason for these differences is not clear; they may not be related to the aetiology of the disease but to a combination of factors, namely: age of the patients, extent and severity of crescent formation and effectiveness of therapy.

It was not possible to assess the response to treatment of patients in the present study since there were only a few patients in any treatment regime. Similarly, it was difficult to evolve a rational approach to therapy since the pathogenesis of this condition is not clearly understood. There are however, reports of satisfactory response to treatment with corticosteroids,[13] anticoagulation,[11] plasmapheresis,[14] and combined therapy.[3 6] The rationale for the use of prednisolone is to inhibit or stop immunological reaction which is believed to precipitate RPGN. Plasmapheresis is used in an attempt to remove circulating immune complexes. The basis for the use of anticoagulants is the detection of fibrin in the area of crescent formation. It is postulated that coagulation in the microvasculature of the kidney is important in the mechanism of injury as well as in the development of crescent.[15 16] Crescent formation has however, been prevented in experimental animals by anticoagulation or defibrination.[17]

These different forms of treatment as outlined above may be effective at different points in the chain of events that culminate in RPGN. Until the pathogenesis of this disease is well understood, there is a strong need for a multicentre controlled trial of combined therapy using plasmapheresis, immunosuppresive drugs and anticoagulants.

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