Crescentic glomerulonephritis in children: a retrospective review of data at Chris Hani Baragwanath Academic Hospital

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Crescentic glomerulonephritis in children: early treatment allows a favourable outcome. A retrospective review of data at Chris Hani Baragwanath Academic Hospital, Soweto.

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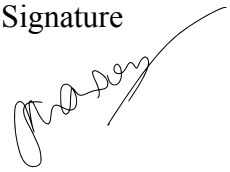
Declaration

I, Sajeda Mansoor, declare that this research report is my own, unaided work. It is being submitted for the degree of MMed Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature



10 day of November 2020 in Johannesburg

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Conflict of interest

None.

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Abstract

Background

Crescentic glomerulonephritis as a cause of progressive renal failure is rare. Crescent formation represent a response to injury of the glomerular capillary walls in patients with crescents on kidney biopsy.

Objectives

Most publications on CGN represent adult patients; with regards to paediatric patients the data is minimal, especially from our setting here in Africa. This study serves to describe the clinical presentation on children with CGN in South Africa.

Methods

A retrospective study was conducted at this hospital over 22 years. Children younger than 14 years with crescent formation in more than fifty percent of glomeruli on renal biopsy were included from data extracted using the renal biopsy register and files.

Results

Fourteen patients (1.5%) met criteria from 961 renal biopsies performed. Kidney biopsy specimens were examined by light microscopy, immunofluorescence and electron microscopy. Common findings were oedema (n=13, 92.9%), microscopic haematuria (n=12, 85.7%), hypertension (n=11, 78.6%) and proteinuria (n=10, 71.4%). The median GFR at presentation was 23.9ml/min/1.73m^2. Thirteen patients (n=13, 93%) had immune-complex mediated glomerulonephritis. The underlying renal pathology was acute post-infectious glomerulonephritis in nine patients (64.3%), membranoproliferative glomerulonephritis and IgA nephropathy in two patients each (14.3%), and global sclerosis in one patient (7.1%).Treatment included peritoneal dialysis, methylprednisone and cyclophosphamide. Seven (n=7, 50%) patients had a normal GFR at a median follow-up of 36 months. Six (42.9%) patients had progressed to chronic kidney disease.

Discussion

This study spanning 22 years demonstrated that 1.5% of total renal biopsies had crescent formation which involved fifty percent or more of glomeruli. The commonest clinical findings are a hallmark of glomerulonephritis. We have documented that cellular and fibrocellular crescents occur most commonly in the patients that were seen at our centre. Indicators of a better outcome are cellular crescents on biopsy findings. The percentage of glomeruli affected by crescents is not associated with a poor prognosis. Poor renal outcomes were observed in patients who presented late. As this was a retrospective study, it posed a limitation as not all patient records were complete. The study population was also very small, and a larger data set will allow for more accurate results. Despite the limitations, the results have important considerations especially with regards to patients having a better outcome if referred timeously. A national database would assist in the recognition and management of this disease.

Conclusion

Early treatment at the time of crescent formation has a better outcome than a delayed diagnosis. We recommend bedside tests such as blood pressure monitoring and urine testing for early recognition of this disease.

Introduction

Crescentic glomerulonephritis (CGN) is a rare condition in childhood[1,2,3,4,5]. It is characterised histologically by the presence of crescents on renal biopsy specimens, and clinically by a sudden and progressive decline in renal function[3,4]. This clinical entity is referred to as rapidly progressive glomerulonephritis (RPGN)[4], figure 1, and was initially described in 1942 by Arthur Ellis[6].

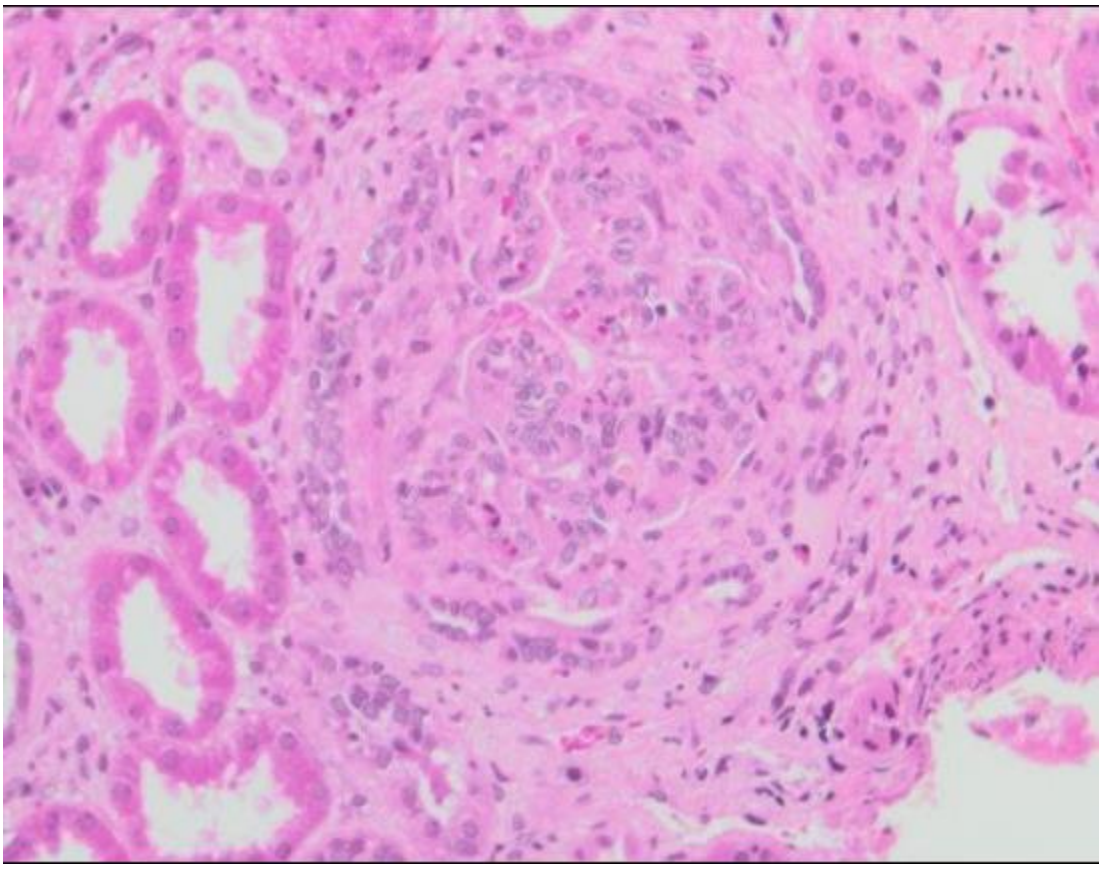

Figure 1 Post-infectious glomerulonephritis; glomerulus illustrating occlusion of capillary loops by swollen endothelial cells as well as occasional neutrophils. This is accompanied by a circumferential cellular crescent. H&E X 200.

Crescent formation accompanies primary glomerulonephritis or systemic disease[3,4]. It is initiated by multiple aetiologies and pathogenic mechanisms[7]. Crescents represents a response to injury of the glomerular capillary walls[8]. Breaks are incurred in the glomerular capillary walls causing plasma products to move into Bowman's space[8]. This causes fibrin formation, an influx of

macrophages and T-cells, and the release of pro-inflammatory cytokines such as IL-1 and TNF-α[8].

Crescents are divided into cellular, fibrocellular or fibrous, according to the World Health Organization classification of glomerular disease[3,4,9,10]. Cellular crescents show a prominent proliferation of epithelial cells with a combination of macrophages and neutrophils filling Bowman's space and compressing the glomerular tuft[4,8]. Fibrocellular crescents occur when strands of membrane-like material and collagen fibres are present amongst the cells forming the crescent[4,9]. Fibrous crescents describe a lesion within Bowman's space composed predominantly of fibrous tissue[9]. Development of fibrocellular and fibrous crescents represent a stage of disease that is unlikely to respond to immunosuppressive therapy[8].

The aetiologies that lead to RPGN are grouped into three main categories[7,10], based on the pattern of immunoglobulin deposition on immune-histological examination[7,11,12,13]. These are: immune-complex mediated, which include post-infectious glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis and IgA nephropathy; pauci-immune, which is commonly attributed to ANCA-associated vasculitis; and anti-glomerular basement membrane disease (anti-GBM)[11,12].

Regarding CGN in paediatric patients, the data is scanty, especially from our setting here in Africa. The largest study published in South Africa was in 1998 by Parag et al[14]. This study was over a period of six years and reviewed 27 cases of CGN from 458 renal biopsies performed in that time (5.9%). The age group was between 12 to 64 years with four patients in the paediatric age from twelve to fourteen years old. In all four paediatric cases immune-complex mediated disease accounted for the aetiology. Cellular crescents were the most common.

A study published in 2007 involving paediatric patients in a developing country was conducted over five years and 5.1% of all renal biopsy specimens in this time frame were CGN[3]. Twenty-two patients were assessed and the most common aetiology was immune-complex mediated disease. Fibrocellular crescents were the most common. The mean follow-up period of patients was 8.13 months.

A recent study in 2015[5], reviewed forty-five patients over eleven years. Cellular crescents were present in the majority of patients. Immune-complex mediated disease was the most common aetiology.

Pauci-immune glomerulonephritis is emerging as a cause of CGN amongst children[1]. Anti-glomerular basement membrane disease is very rare in children. A study over twenty-five years showed four cases of anti-GBM disease[15].

Studies have shown that between 19.4% and 46.2%[1,3,4,5,16] of patients had a normal GFR at follow-up.

There are no publications to date on CGN in children in South Africa. This study serves to describe the clinical presentation, patient outcome and response to therapy on children with CGN in South Africa.

Study design

A retrospective, observational study was conducted at this hospital, which is situated in Soweto, Johannesburg, South Africa. This is the largest hospital in the southern hemisphere, serving a population of 1.27 million people[17].

The study period was conducted between 01 January 1990 up until 30 June 2012. Paediatric patients up to the age of fourteen years were assessed. Patients were included in the study if they met the definition of crescentic glomerulonephritis, which is crescent formation which involves fifty percent or more of glomeruli on renal biopsy.[3]

Definitions that were used in this study are summarised in Table 1.

Table 1 Definitions used in this study

Hypertension	Systolic and/or diastolic blood pressure that is equal to or greater than the 95th percentile (on the basis of age, sex and height percentiles) based on the Paediatric Task Force recommendations[18]
Proteinuria	As evaluated by urine dipstick examination (2+ protein or greater detected)[9], or a urine protein:creatinine ratio

Haematuria	As evaluated by urine dipstick examination, or if visible to the naked eye[9]
Oliguria	Urine output that is less than 1ml/kg/hour in infants, or less than 0.5ml/kg/hour in children[19]
Acute kidney injury was defined using the KGIDO guidelines[20]	Increase in serum creatinine by ≥ 26.5micromol/l within 48 hours or Increase in serum creatinine ≥1.5 times baseline which is known or presumed to have occurred within the past seven days or Urine volume < 0.5ml/kg/hour for six hours
Glomerular filtration rate - Calculated from the Schwartz estimate[21,22]	GFR (ml/min/1.73m^2) = (k X height)/serum creatinine (mg/dL) Where k = 0.33 for age less than 1 year and low birth weight less than 2500g k = 0.45 for age less than 1 year and birth weight greater than 2500g k = 0.55 for a child or an adolescent female k = 0.70 for an adolescent male
Staging of GFR (ml/min/1.73m^2)[23]	Chronic kidney disease (CKD) Stage GFR (ml/min/1.73m^2) CKD stage 1 ≥ 90 CKD stage 2 60 to 89 CKD stage 3 30 to 59 CKD stage 4 16 to 29 CKD stage 5 < 15
Height and weight	Plotted using the Centers for Disease Control and Prevention growth charts [24].

Stunting	Height which plotted below the 5th centile
GFR recovery	The difference between GFR at presentation and at follow-up

Creatinine was performed by the National Health Laboratory using the Jaffé method, the original Schwartz formula was used to calculate GFR. The machine used is the Roche Cobas c8000 which is manufactured in Germany. It is an in vitro test for the quantitative determination of creatinine in human serum, plasma and urine. The test principle is based on the Jaffé method[25].

Statistical analysis

Continuous variables were represented by a mean, median, range and interquartile range (IQR). Categorical data were represented by linear regression graphs and normal distribution graphs. Statistical analysis was performed by the statistical software STATA 14.2. The value $P < 0.05$ was considered as statistically significant.

Methods

The paediatric Renal Department maintains records of all renal biopsies and this register was used to identify patients with crescentic glomerulonephritis. These patients renal and ward files were reviewed for the data: gender, age, height, clinical findings, duration of symptoms before presentation to a health care facility, glomerular filtration rate at presentation, time taken for a renal biopsy to be performed, renal biopsy findings, treatment initiated, duration of time from presentation until treatment was initiated, follow-up visit signs and symptoms and glomerular filtration rate.

Due to the retrospective nature of the study, although there was no standardization of weight, height and blood pressure monitoring, these measurements were recorded by paediatric staff.

Renal biopsy results were extracted from the National Health Laboratory Service (NHLS) system. The renal biopsy results are reviewed at a monthly histopathology meeting. Follow-up is

the latest documented follow-up visit to the hospital as at 30 June 2012. The results are reported using the STROBE guidelines[26].

Results

A total of 961 renal biopsies were performed during this time period. Seventy eight (8.1%) of these biopsies had evidence of crescent formation. Of these patients with evidence of crescent formation, fourteen (1.5%) had crescents in fifty percent or more of glomeruli visible on biopsy, figure 2.

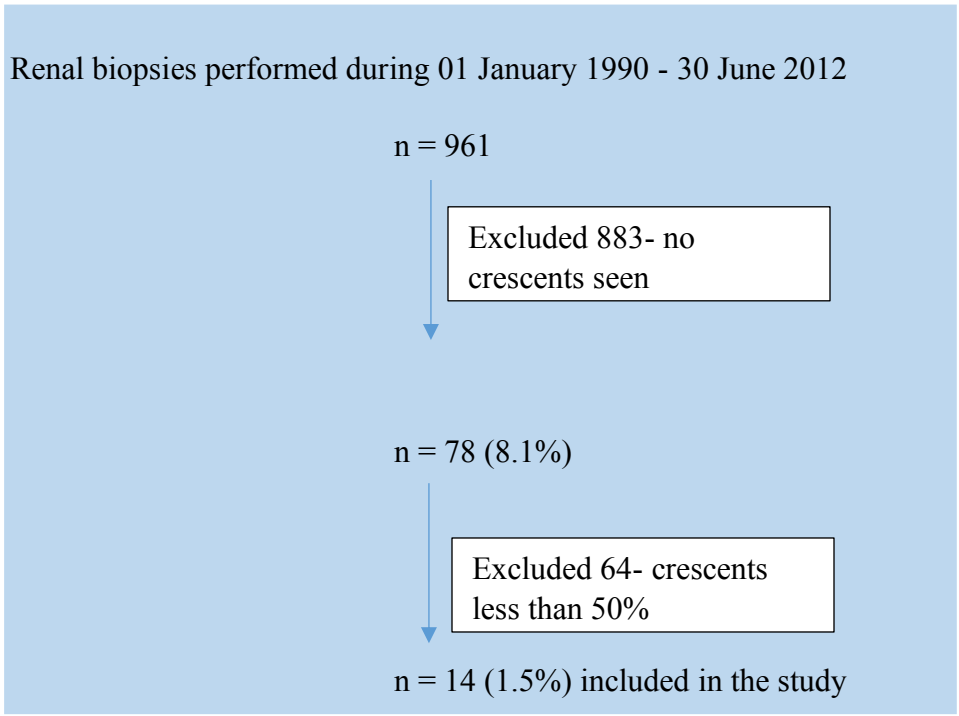

Figure 2 – Renal biopsies performed during the 22-year study period

Fourteen patients were identified in this study, eight patients (57.1%) were female. All files were accounted for, however there was missing information from certain files.

The median age at presentation was 123 months (range 49 - 164, IQR 81.5 - 144.5). The median height was 130cm (range 94 - 187, IQR 117.8 - 137.5) and the median weight was 28.9kg (range 12.6 - 64, IQR 21.7 - 43.7). Three patients (21.4%) were underweight and four patients (28.6%) were stunted.

Tables 2 and 3 summarises the demographics, presenting features, clinical findings and blood results with which patients presented.

Table 2 – Patient demographics, presenting features and clinical findings

Gender	**n (%)**
Males	6 (42.9%)
Females	8 (57.1%)
Age groups	**n (%)**
Under 5 years of age	2 (14.3%)
5 – 10 years of age	5 (35.7%)
Older than 10 years of age	7 (50%)
Presenting symptoms (some overlap)	**n (%)**
Oedema	10 (71.4%)
Macroscopic haematuria	6 (42.9%)
Oliguria	5 (35.7%)
Skin lesions	2 (14.3%)
Nausea and vomiting	2 (14.3%)
Haemoptysis	1 (7.1%)
Haematemesis	1 (7.1%)

Clinical findings (some overlap)	**n (%)**
Oedema	13 (92.9%)
Microscopic haematuria	6 (42.9%)
Macroscopic haematuria	6 (42.9%)
Hypertension	11 (78.6%)
Proteinuria	10 (71.4%)
Oliguria	5 (35.7%)
Median GFR (ml/min/1.73m^2)	23.9 (range 3.3 - 86.4, IQR 9.0 - 49.1)

The duration of symptoms was unknown for two patients (14.3%), and one patient (7.1%) was excluded from these data calculations. The median duration of symptoms was seven days (range 1 - 30, IQR 3 - 14). Thirteen patients (92.3%) presented with acute renal injury.

Table 3 – Blood results of patients

Blood tests	**n (%)**	**Aetiology**			
Antinuclear antibody (ANA)		**APIGN**	**IgA nephropathy**	**MPGN**	**Global sclerosis**
Positive	0	0	0	0	0
Negative	7 (50%)	4	1	1	1
Test not done	7 (50%)	5	1	1	0
Antineutrophil cytoplasmic antibodies (ANCA)					
Positive	0	0	0	0	0
Negative	3 (21.4%)	1	0	2	0
Test not done	11 (78.6%)	8	2	0	1
Antistreptolysin O Titer					
Normal	5 (35.7%)	2	0	2	1
Increased	8 (57.1%)	6	2	0	0
Test not done	1 (7.1%)	1	0	0	0
Median value 287IU (range 95 – 1480, IQR 142.5 – 579)					

Blood tests n (%)		**Aetiology**			
HIV ELISA		**APIGN**	**IgA nephropathy**	**MPGN**	**Global sclerosis**
Negative	9 (64.3%)	6	2	1	0
Positive	0	0	0	0	0
Test not done	5 (35.7%)	3	0	1	1
Complement C3					
Normal	7 (50%).	3	2	1	1
Decreased	7 (50%)	6	0	1	0
Complement C4					
Normal	13 (92.9%)	9	2	1	1
Decreased	1 (7.1%)	0	0	1	0
Total albumin					
Normal	1 (7.1%)	0	0	0	1
Decreased	11 (78.6%)	7	2	2	0
Test not done	2 (14.3%)	2	0	0	0
Anti-glomerular basement membrane (anti-GBM) antibodies					
Not tested					

APIGN- acute post infectious glomerulonephritis MPGN- membranoproliferative glomerulonephritis

The median GFR was 23.9ml/min/1.73m^2 (range 3.3 - 86.4, IQR 9.2 - 49.1) at presentation. A regression fit model was created to ascertain if there was a relationship between GFR recovery and the duration of symptoms. There is an inverse relationship on the graph between the two variables seen in Figure 3, however the relationship is not statistically significant with a p-value of 0.105.

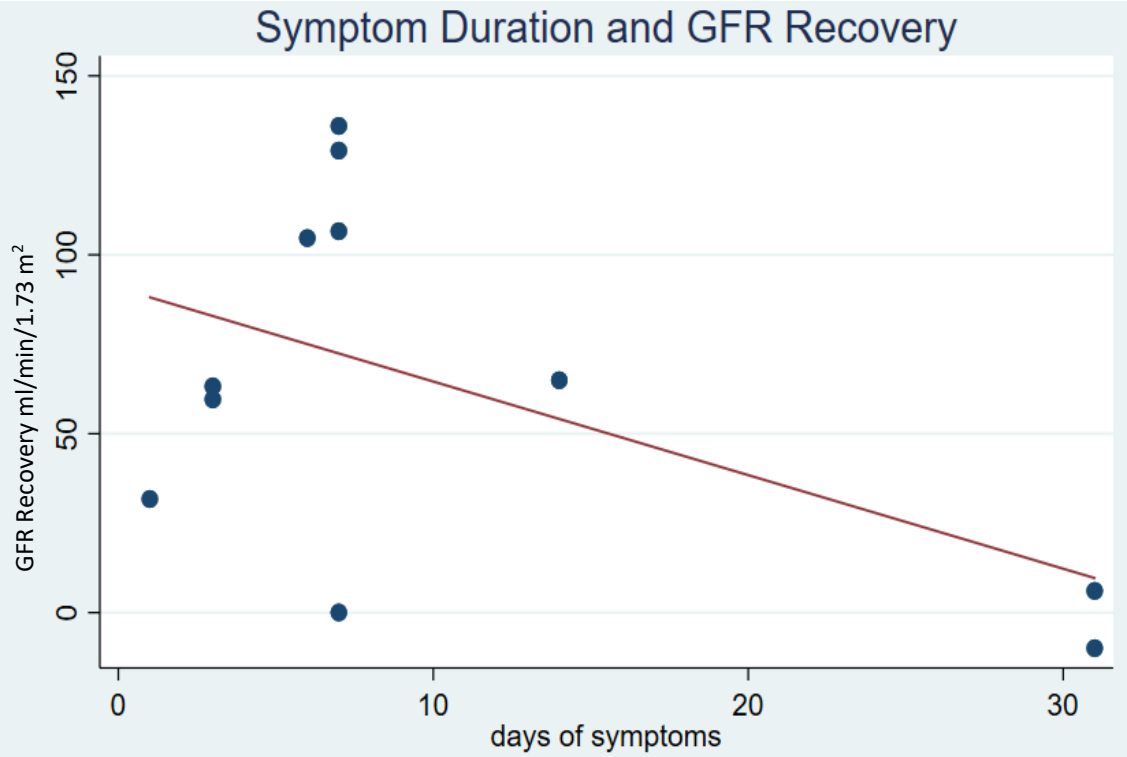

Figure 3 – Relationship between GFR at presentation and follow-up and symptom duration

The median duration of admission was 38.5 days (range 20 - 121, IQR 22.5 - 53).

Renal biopsies were performed on a median of 12 days from admission to hospital (range 2 - 34, IQR 7 -19). Adequate renal biopsies should contain at least ten glomeruli for light microscopy[27]. Histopathological examination was processed by light microscopy, immunofluorescence and electron microscopy. Thirteen (92.9%) specimens had data on the number of glomeruli seen on light microscopy on renal biopsy. The median number of glomeruli is 26 (range 5 – 100, IQR 19 – 46.5). Twelve (85.7%) specimens had greater than ten glomeruli visible on light microscopy.

Renal biopsy findings are summarised in Table 4.

Patients with fibrocellular and cellular crescents have a GFR recovery which is greater than 50ml/min/1.73m^2, while patients with fibrous crescents have an improvement in GFR by more than 30ml/min/1.73m^2.

Table 4 – Histology findings

Crescents	**n (%)**
50-59%	3 (21.4%)
60-79%	6 (42.9%)
80-100%	5 (35.7%)
Types of crescents (some overlap)	**n (%)**
Cellular	12 (85.7%)
Fibrocellular	11 (78.6%)
Fibrous	2 (14.3%)

Thirteen patients (n=13, 93%) had immune-complex mediated glomerulonephritis (see Table 5).

Table 5 – Underlying renal pathology in CGN

	n (%)
Total number of patients with CGN	14
Acute post-infectious glomerulonephritis (Figure 4)	9 (64.3%)
Membranoproliferative glomerulonephritis	2 (14.3%)
IgA nephropathy	2 (14.3%)
Indeterminate cause - global sclerosis	1 (7.1%)

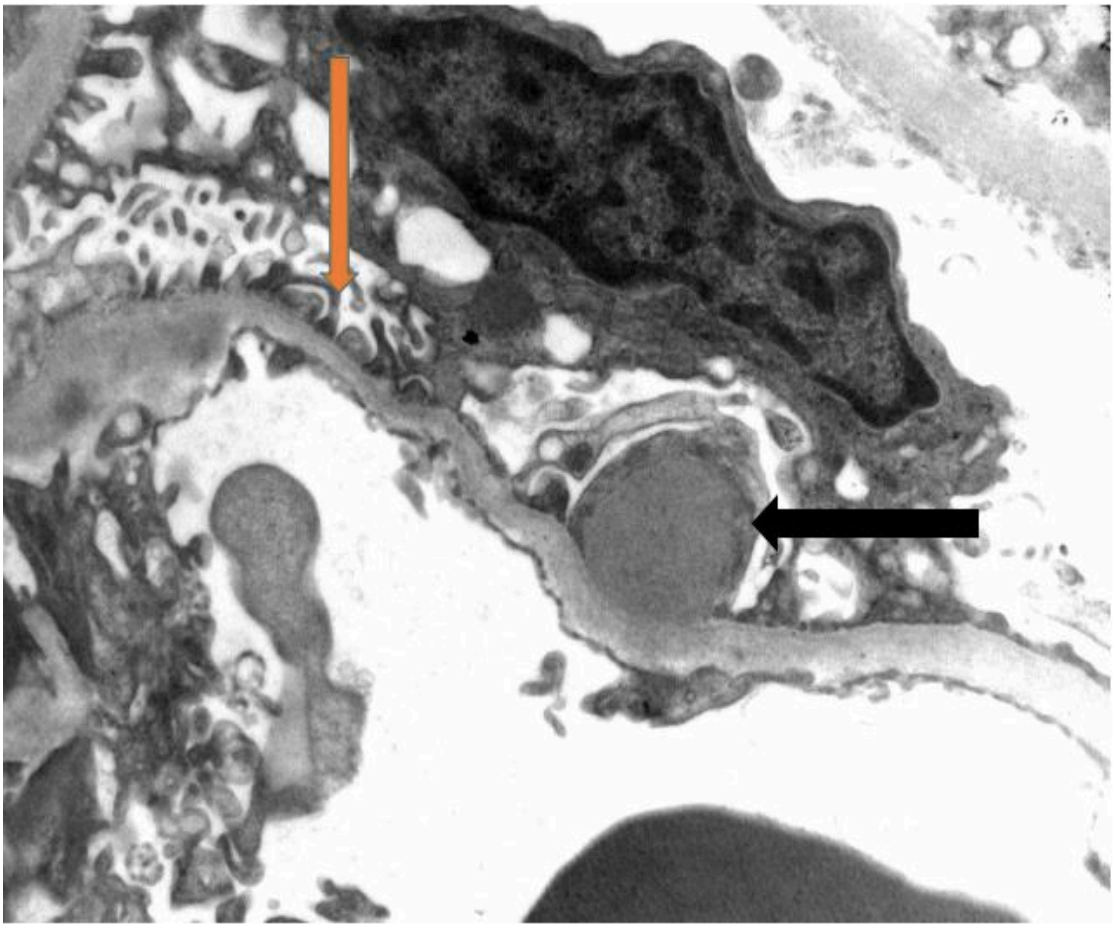

Figure 4 Post-infectious glomerulonephritis; An electron micrograph illustrating an electron dense subepithelial “hump” (black arrow). The podocyte foot processes are maintained and not effaced (orange arrow). Mag X12000.

Treatment

Treatment included renal replacement therapy, which constituted peritoneal dialysis, methylprednisone and cyclophosphamide. One patient (7.1%) was treated with methylprednisone, and two patients (14.3%) were treated with cyclophosphamide. Nine patients (64.3%) were treated with both agents.

Six patients required renal replacement therapy with peritoneal dialysis. Five of these patients had commenced dialysis prior to their renal biopsies being performed. The median duration of dialysis was 28 days (range 8 - 116, IQR 11.5 - 77.5). Of these six patients, one patient (16.7%)

demised, one patient (16.7%) was well and the remaining four patients (66.6%) were lost to follow-up.

Treatment is unknown for one (7.1%) of the patients.

The median duration from the onset of symptoms to treatment is 19.5 days (range 8 - 42, IQR 10.5 – 33.5). The time of initiation of treatment is unknown for two patients. For the remaining twelve patients, one (8.3%) patient commenced treatment prior to their renal biopsy being performed.

The data is known for thirteen patients in respect to the time period from when patients presented to the initiation of treatment. The median duration from the time of presentation to treatment is 10 days (range 0 - 35, IQR 2 - 17.5).

Outcome

The median duration of follow-up was 12 months 4.5 days (range 1 month 2 days – 72 months 9 days, IQR 4 months 22 days – 54 months 20 days). The median age at follow-up was 128 months (range 54 - 208, IQR 105.5 - 178).

At follow-up visitation seven (50%) patients had a normal function, Table 6. These patients followed up for a median time of 36 months 22 days (range 4 months 16 days – 61 months 15 days, IQR 10 months 15 days – 55 months 13 days). Six (42.9%) patients had progressed to chronic kidney disease. One (7.1%) patient had CKD 2, one (7.1%) patient had CKD 4, and four patients (28.6%) patients had CKD 5. One (7.1%) patient had a follow-up of less than three months. The median GFR was 89.7 ml/min/1.73m^2 (range 3.8 - 175, IQR 12.7 - 140.4). At follow-up nine patients (64.3%) had a normal weight, and ten patients (71.4%) had a normal height. The weight at follow-up was unknown for two patients.

Table 6 – Outcome of patients with CGN

Treatment	**Staging of CKD using GFR (ml/min/1.73m^2 at follow-up)**					
	1	**2**	**3**	**4**	**5**	**Outcome**
MP and CP (n=5)	3	0	0	0	2	Discharged to follow-up (n=5)
CP (n=1)	1	0	0	0	0	Discharged to follow-up (n=1)
MP (n=1)	1	0	0	0	0	Discharged to follow-up (n=1)
Dialysis, MP and CP (n=4)	2	1	0	0	1	Discharged to follow-up (n=3)
						Demised (n=1)
Dialysis and CP (n=1)	0	0	0	1	0	Discharged to follow-up (n=1)
Dialysis (n=1)	0	0	0	0	1	Did not return (n=1)
Unknown (n=1)	0	0	0	1	0	Demised (n=1)
						Had a follow-up of less than three months.

MP – methylprednisone CP - cyclophosphamide

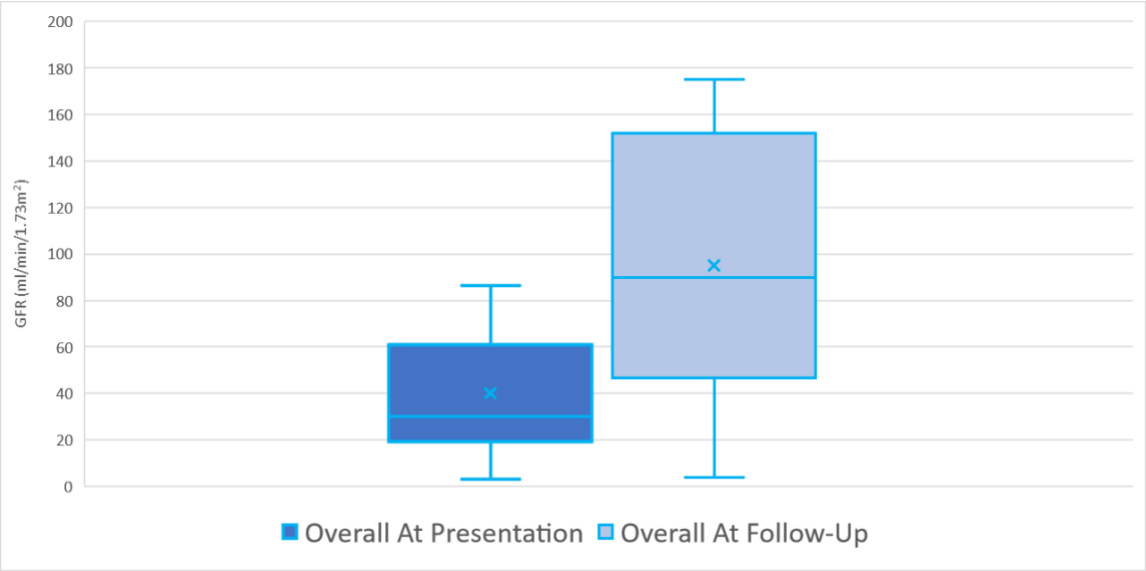

Figure 5 – GFR at presentation and follow-up

Figure 5 shows a box and whisker plot of GFR at presentation and at follow-up. The median GFR at presentation was 23.9ml/min/1.73m^2 (range 3.3 - 86.4, IQR 9.2 - 49.1), and at follow-up the median GFR was 89.7 ml/min/1.73m^2 (range 3.8 - 175, IQR 12.7 - 140.4). The median GFR had improved significantly.

A linear regression was plotted between the percentage of glomeruli which had crescents and GFR recovery. There is no relationship between the percentage of glomeruli affected by crescents and the GFR recovery, Figure 6. The p-value is 0.756.

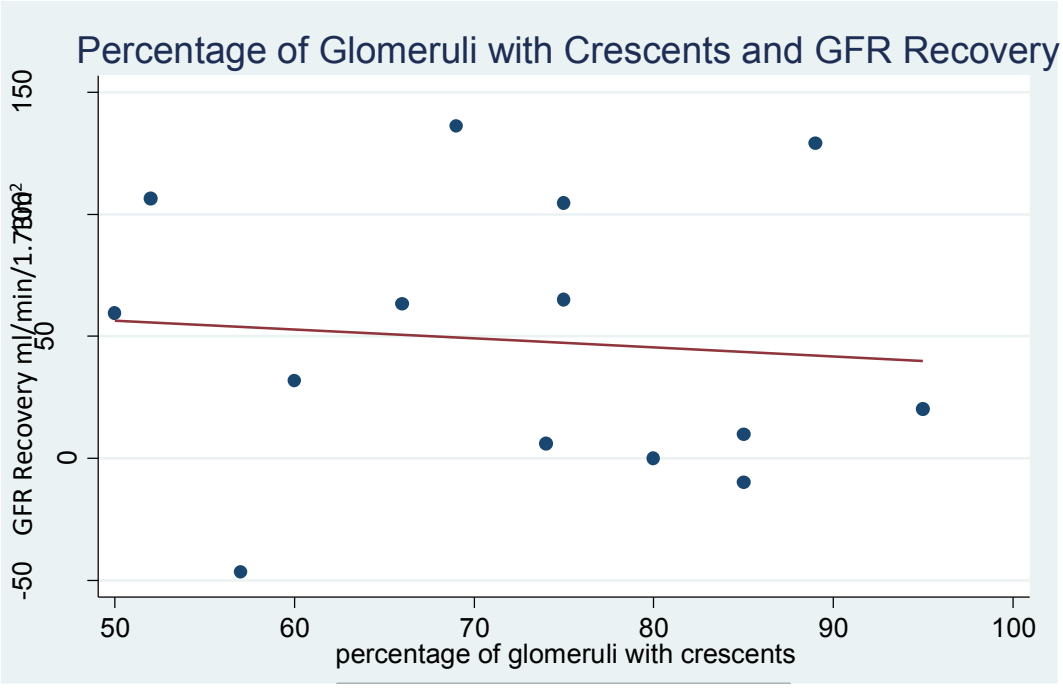

Figure 6 – Relationship between the percentage of glomeruli with crescents and GFR recovery

Two patients showed a decrease in GFR between presentation and follow-up. The median GFR recovery between presentation and follow-up was 45.7 ml/min/1.73m^2 (range -46.81 - 136, IQR 3.1 - 105.6).

Residual sequelae

Nine patients (64.3%) had hypertension, eight patients (57.1%) had proteinuria, and seven patients (50%) had microscopic haematuria. The median duration of follow-up was 12 months 4.5 days (range 1 month 2 days – 72 months 9 days, IQR 4 months 22 days – 54 months 20 days). The long-term follow up rate of our patients was very poor (64.3%) as most of them presented for follow-up initially, then did not continue with their scheduled appointments. One patient continued follow up after June 2012 when the study period ended.

Two (14.3%) patients demised.

Discussion

CGN is uncommon in children. This study spanning 22 years demonstrated that 1.5% of total renal biopsies had crescent formation which involved fifty percent or more of glomeruli. The incidence of CGN varies with the location and policies of renal biopsies[28].

The mean age at presentation was 113 months. This is similar to other reports[1,4,5,9]. There were two (14.3%) patients under the age of five years. CGN in patients under the age of four years is unusual[8]. This may be attributed to young children not acquiring full immunity as yet. Most of our patients demonstrated a normal nutritional status. Eleven patients (78.6%) had a weight which plotted between the normal centiles. Ten patients (71.4%) had a height which plotted between the normal centiles. This illustrates that the majority of CGN is not a chronic disease. At follow-up nine patients had a weight which plotted between the normal centiles and ten patients had a height which plotted between the normal centiles. It is possible that oedema affected the weight of patients, but not the height.

The commonest clinical findings are a hallmark of glomerulonephritis. Eleven patients were found to be hypertensive. Urine dipstick examination was positive for microscopic haematuria in twelve patients, and positive for proteinuria in ten patients. Other series are consistent with the above as presenting signs[4,8,16]. These signs should be specifically looked for in bedside tests.

Oliguria was not a common feature in patients in this study. It was stated in a study that a period of prolonged oliguria separates RPGN from acute glomerulonephritis[16]. Five (35.7%) patients presented with this complaint, compared to between 50% to 86.4%[1,3,4] in other studies. This could be attributed to patients presenting early on in the course of the disease, the nature of the study being retrospective, or poor documentation of symptoms.

All patients, excluding the patient described earlier, presented in acute kidney injury. All patients had renal biopsies performed within a period of 2 days - 34 days. The delay in renal biopsies were as a result of patients being critically ill and unstable for theatre.

Six (66.7%) patients with APIGN had a decreased C3 and a positive ASOT titre. No patients had ANA positivity, and anti-GBM antibodies were not tested for. As this study was conducted between 1990 - 2012, ANCA assays, ANA and anti-GBM antibodies were not readily available. Twelve (85.7%) patients had hypoalbuminaemia. In kidney disease the aetiology of

hypoalbuminaemia is multifactorial[29]. Hypoalbuminaemia is associated with a decreased GFR[29] and with urinary losses of albumin[30]. Reduced synthesis of albumin may be a result of anorexia due to uremia[31].

Blood tests were performed based on the clinical suspicion of the underlying renal pathology causing CGN.

Most patients (85.7%) had cellular crescents. Other studies have demonstrated the majority of crescents being fibrocellular[3,8,9]. Cellular crescents indicate that the lesions are in the early stages of formation, and also indicates that patients presented early. Fibrous crescents are associated with a poor outcome[4,9], and gives an indication of the chronicity of the disease.

We have documented that cellular and fibrocellular crescents occur most commonly in the patients that were seen at this center, and these types of crescents have a better outcome in terms of GFR recovery. The percentage of glomeruli affected by crescents is considered a poor prognostic feature[9]. In this study there was no evidence to support this. Based on the data at this hospital, the percentage of crescents did not affect recovery in GFR. This finding was similar to other studies[4,9].

Sixty four percent of cases had an underlying renal pathology of post-infectious glomerulonephritis as a cause for CGN. Similar results were found in the study by Dewan et al[3], where fifty percent of cases also had post-infectious glomerulonephritis; and by Parag et al[14], where one hundred percent of paediatric cases of CGN were of post-infectious pathology. These studies were conducted in developing countries. Studies in other areas of the world have found lupus nephritis as a common cause in 54.1% of their cases[32]. Most patients (93%) in this study had an immune-mediated cause for CGN, and the majority of the literature had similar results[3,4,5,9,16]. Pauci-immune was a common cause of CGN in 52.8%[1] and 63.3%[33] of patients in other studies. In China and Macedonia there is a higher incidence of immune-complex mediated glomerulonephritis, and this was attributed to the high prevalence of infection with nephritogenic strains in these regions[2]. Primary diseases that develop CGN show regional variation[28].

Fifty percent of patients had a normal GFR at follow-up compared to other studies. The patients in this series with a normal GFR had a follow-up period for a median time of 36 months 22 days. The mean follow-up period of patients were 8.13 months[3], 24 months[4] and a median of 34 months[1] in other studies.

The initial GFR correlating well with the final GFR may be attributed to early diagnosis and initiation of treatment. The need for early treatment is emphasized as this is not a self-limiting disease. The best predictor of outcome is the severity of renal failure at the time of commencement of therapy[5,7]. A few days in the delay in diagnosis and treatment may have a negative impact on outcome as a result of the rapidly progressive loss of renal function[7].

This study has a good recovery in terms of GFR for a developing country. This could be attributed to the majority of our patients presenting within a week of symptom onset, and the majority of crescents still being in the early phase of development.

As this was a retrospective study, it posed a limitation as not all patient records were complete. The study population was also very small, and a larger data set will allow for more accurate results. This may be difficult to carry out as crescentic glomerulonephritis is an uncommon disease. There was non-adherence of patients to scheduled follow-up visitations. This has been documented and is due to a mobile population, lack of funds for travel to health facilities, inadequate housing and inadequate nutrition[34].

This data set is based on a small group of patients, and the results obtained may act as a foundation for further studies.

Despite the limitations, the results have important considerations especially with regards to patients having a better outcome if referred timeously.

A national database would assist in the recognition and management of this disease, as was found by Koyama et al[35], where after the results of their national survey on RPGN were announced, recognition of this disease was improved in general practice.

Conclusion

The symptoms with which patients presented to the hospital were indicative of a glomerulonephritis. The associated renal failure raised suspicion for CGN. We have demonstrated that indicators of a better outcome are cellular crescents, which is in the early stages of formation. Patients who present earlier have a higher GFR at presentation, and there is

a relationship with a higher GFR at follow-up. The percentage of glomeruli affected by crescents did not impact outcome.

A national database would assist in the recognition and management of this disease. It is important that a greater awareness of this disease is brought about amongst paediatricians and general practitioners. Early diagnosis is imperative in patients with CGN as this is a disease in which the renal function deteriorates rapidly. Bedside tests such as blood pressure monitoring and urine testing are important as they provide immediate results which aid in the diagnosis of a patient. These patients should be referred promptly to a renal center, especially from centers where a delay in obtaining laboratory results may negatively impact the outcome.

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Appendix A – patient information

Study number	Gender	Age at presentation	Hypertension	Oedema	Oliguria	Proteinuria	Microscopic haematuria	Macroscopic haematuria
1	F	4y10m	Yes	Yes	No	Yes	Yes	Yes
2	F	9y11m	No	Yes	No	Yes	Yes	No
3	F	8y2m	Yes	Yes	Yes	Yes	Yes	No
4	M	7y9m	Yes	No	No	No	Yes	Yes
5	F	11y	Yes	Yes	No	Yes	Yes	No
6	M	4y1m	Yes	Yes	No	Yes	Yes	Yes
7	M	10y7m	Yes	Yes	No	Yes	Yes	Yes
8	M	7y	No	Yes	Yes	No	Yes	No
9	M	13y8m	Yes	Yes	Yes	Yes	Yes	Yes
10	F	12y3m	Yes	Yes	No	Yes	Yes	No
11	F	13y6m	No	Yes	No	No	No	No
12	M	6y7m	Yes	Yes	Yes	Yes	Yes	Yes
13	F	10y11m	Yes	Yes	Yes	Unknown	Unknown	Unknown
14	F	11y10m	Yes	Yes	No	Yes	Yes	No

Appendix A – patient information

Study number	Percentage of crescents	Type of crescents	Cause	Renal biopsy prior to commencement of treatment	Protein	Albumin
1	85	Cellular-fibrocellular	Post infectious	Yes	Test not done	Test not done
2	74	Cellular	Post infectious	Unknown	58	24
3	75	Cellular-fibrocellular	Post infectious	Yes	62	28
4	50	Fibrocellular	Ig A nephropathy	Yes	Test not done	31
5	60	Cellular-fibrocellular	Ig A nephropathy	Yes	Test not done	33
6	66	Cellular-fibrocellular-fibrous	Post infectious	Yes	Test not done	27
7	52	Cellular-fibrocellular	Post infectious	Yes	Test not done	26
8	85	Cellular-fibrocellular	Post infectious	Unknown	65	27
9	89	Cellular	Post infectious	Yes	61	27
10	69	Cellular-fibrocellular	MPGN	Yes	55	22
11	>80	Fibrocellular-fibrous	Chronic GN	Yes	76	37
12	75	Cellular-fibrocellular	Post infectious	Yes	Test not done	Test not done
13	95	Cellular-fibrocellular	Post infectious	Yes	Test not done	28
14	57	Cellular	MPGN	No	45	18

Appendix A – patient information

Study number	Urine MC&S	Urine protein: creatinine ratio (g/mmol)	Blood	Protein	Plasma sodium (mmol/l)/ potassium (mmol/l)	Renal replacement therapy	Days of renal replacement therapy	Outcome
1	Test not done	Test not done	4+	2+	137/ 5.5	No	-	Demised
2	Test not done	Test not done	3+	3+	148/ 6	No	-	Lost to follow-up
3	Negative	0.84	4+	2+	126/ 4.2	No	-	Well
4	Test not done	Test not done	4+	-	143/ 3.5	No	-	Lost to follow-up
5	Test not done	Test not done	2+	1+	123/ 4.4	No	-	Well
6	Test not done	Test not done	3+	2+	139/ 4.1	No	-	Lost to follow-up
7	Negative	Test not done	4+	1+	139/ 4.4	No	-	Lost to follow-up
8	Negative	Test not done	3+	-	125/ 5.5	Yes	39	Lost to follow-up
9	Test not done	0.19	Not quantified	2+	133/ 6.7	Yes	8	Well
10	Negative	1.31	2+	2+	135/ 3.2	Yes	17	Lost to follow-up
11	Negative	Test not done			134/ 4.6	Yes	116	Demised
12	Test not done	Test not done	4+	2+	141/ 4.3	Yes	15	Lost to follow-up
13	Negative	Test not done			132/ 8	Yes	Unknown	Lost to follow-up
14	Test not done	0.5	4+	2+	141/ 5.2	No	-	Lost to follow-up

Urine MC&S – urine microscopy, culture and sensitivity

Appendix B – ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sajeda Mansoor

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190289

NAME: (Principal Investigator)	Dr Sajeda Mansoor
DEPARTMENT:	Paediatric Renal Unit
PROJECT TITLE:	Crescentic Glomerulonephritis in Children: a review of data at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	30/11/2012 (Initial approval)
DECISION:	Approved unconditionally
CONDITIONS:	Renewal for 5 years Valid for the period 01 February 2019 - 31 January 2024 Previously M121160
SUPERVISOR:	
APPROVED BY:	CB Penny Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/02/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C – protocol

Protocol for

Crescentic glomerulonephritis in children: a review of data at Chris Hani Baragwanath Hospital

Principal investigator: Dr Sajeda Mansoor

MMed (Paediatrics)

Student number: 684781

Contents

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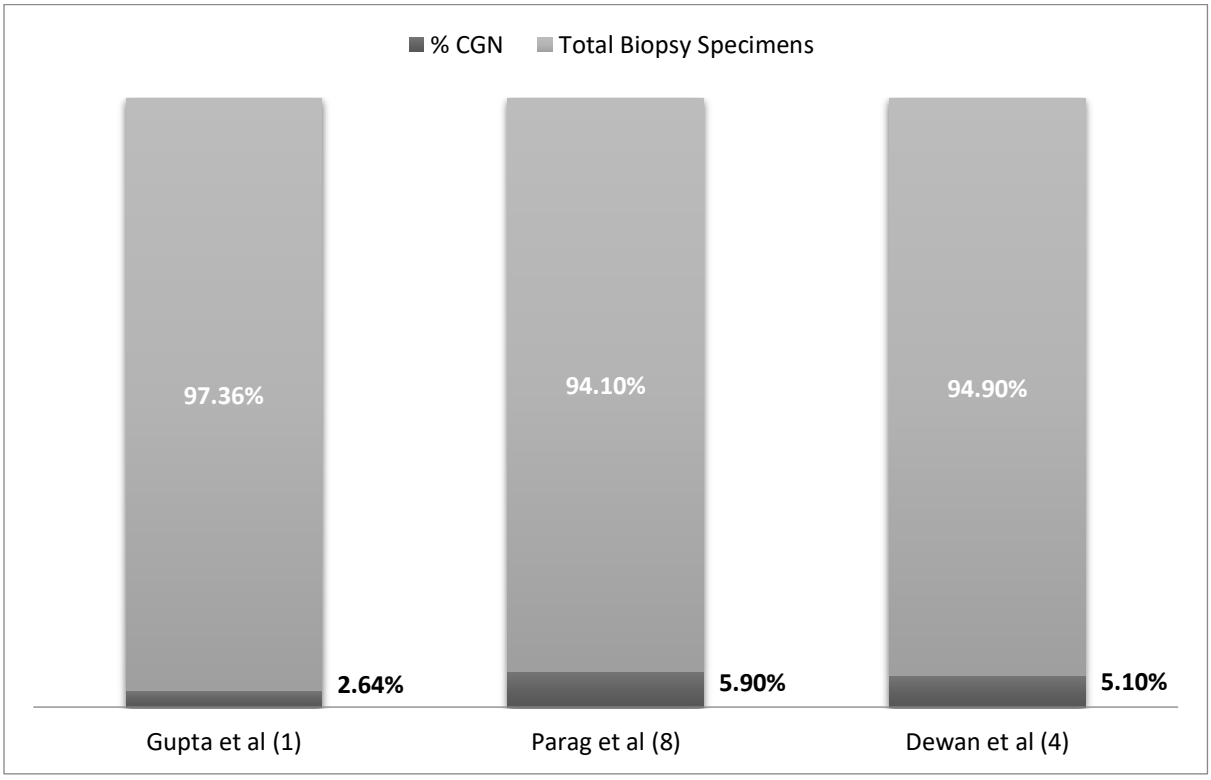
Introduction

Crescentic glomerulonephritis (CGN) is one of the leading histopathological aetiologies that lead to progressive renal failure (1). Histologically, it is characterised by the presence of extensive crescents in renal biopsy specimens. It is characterised clinically by an acute nephritic syndrome with development of end stage kidney disease (ESKD) within a period of a few days to a few weeks. This clinicopathological association is referred to as rapidly progressive glomerulonephritis (RPGN) (2). This entity was initially described in 1942 by Arthur Ellis (3), who described a progressive course of renal failure clinically associated with a histological finding of a progressive stage of an acute lesion within the glomeruli. He described this syndrome as having one of two courses: a rapidly progressive course with death in a few weeks or months, or a very chronic course persisting over years. CGN is a rare entity in children, the graph below emphasises this, showing a percentage of CGN from total renal biopsies done.



CGN can accompany most forms of primary glomerulonephritis but is also associated with various systemic diseases.

CGN is classified into three subtypes histologically (1):

- Anti – glomerular basement membrane antibody disease
- Immune complex mediated glomerular disease
- Pauci – immune glomerular disease

Crescent formation appears to represent a response to injury of the glomerular capillary walls. Breaks are incurred in the glomerular capillary walls causing plasma products to move into Bowman's space. This causes fibrin formation, an influx of macrophages and T – cells, and the release of pro – inflammatory cytokines such as IL – 1 and TNF – α. Development of fibrocellular and fibrous crescents follow this stage of acute inflammation. This is a clinically important stage because fibrous crescents represent a stage of disease that is unlikely to respond to immunosuppressive therapy (5).

Crescents are divided into cellular, fibrocellular or fibrous, according to the World Health Organization classification of glomerular disease (2, 6, 7). Cellular crescents show a prominent proliferation of epithelial cells with a combination of macrophages and neutrophils filling the urinary space and compressing the glomerular tuft. Fibrocellular crescents occur when strands of membrane – like material and collagen fibres are present amongst the cells forming the crescent. Fibrous crescents describe a lesion within Bowman's space composed predominantly of fibrous tissue.

The majority of publications on CGN are on adult patients; with regards to paediatric patients the data is scanty; even more so from our setting here in Africa. The largest study done in South Africa was in 1998 by Parag et al (8). This study was done over a period of 6 years and reviewed 27 cases of CGN from 458 renal biopsies done in that time (5.9%). The age group was between 12 to 64 years with 4 patients falling into the age group for paediatrics: three 12 year old patients and one 14 year old patient. Presenting features common in the group as a whole were hypertension and oliguria. Poststreptococcal glomerulonephritis accounted for 30% of aetiology, anti – glomerular basement membrane disease 15% and idiopathic causes in 33%. 56% of patients had crescents in more than 80% of glomeruli with the remainder having crescents that affected 50 to 80% of glomeruli. Cellular crescents were the most common, followed by fibrous crescents.

A recent study published in 2007 and assessing paediatric patients in developing countries re-enforced the above study (4). This study was conducted over 5 years and 5.1% of all renal biopsy specimens in this time frame were CGN. 22 patients were assessed and the most common aetiologies were postinfectious glomerulonephritis, poststreptococcal glomerulonephritis, mesangiocapillary glomerulonephritis and anti – glomerular basement membrane disease. Hypertension and oliguria were common presenting complaints. 36% of patients had crescents involving more than 80% of glomeruli with 64% of patients having between 50 to 80% of glomeruli affected. Fibrocellular crescents were visible in 64% and fibrous crescents in 46% of patients.

Presentations in countries outside of the African continent were similar with hypertension and oliguria as common features, as well as oedema and macrohaematuria being equally important. Studies from non – African countries reveal that common aetiological causes are systemic lupus erythematosus, poststreptococcal glomerulonephritis, IgA nephropathy and Henoch – Schönlein purpura (2, 5, 6).

The heterogeneity and poor outcome of children with CGN have resulted in multiple treatment regimens consisting of immunosuppressants, anti – platelet drugs, plasma exchange, dialysis and supportive care. Literature reports an excellent outcome in poststreptococcal glomerulonephritis with supportive management (2, 6, 9). However, a few studies have highlighted the progression to renal failure in these children (2, 10). Studies concede that the presence of oliguria on admission is associated with a poor outcome (2, 6, 8, 9, 11) and the presence of greater than 80% of crescents or fibrous crescents pointed toward a poorer prognosis (2, 5, 6).

Aims

1. Clinical presentation of patients with CGN, including signs and symptoms of oliguria, oedema, haematuria, proteinuria and hypertension; and blood results, including urea, creatinine, albumin, C3, C4, antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), antistreptolysin-O titre (ASOT), anti-glomerular basement membrane protein (anti-GBM protein) and human immunodeficiency virus (HIV).
2. Patient outcome with regard to glomerular filtration rate at presentation.
3. Assess response to therapy.

Study design

A retrospective study will be conducted, analyzing data from renal biopsies done at Chris Hani Baragwanath Hospital, which is situated in Soweto, Johannesburg. Chris Hani Baragwanath Hospital is the largest hospital in Africa, accommodating a population of approximately 1.3 million people (12).

Methodology

1. Data will be extracted from the renal biopsy register at Chris Hani Baragwanath Hospital from 01 January 1990 to 30 June 2012. There will be data extraction from two time periods: prior to the diagnostic renal biopsy and at the time of the latest follow up as at 30 June 2012.
2. Children up to 14 years of age will be reviewed.
3. Renal biopsies showing 50% or more of glomeruli involved by crescents will be reviewed. Crescents will be classified into 3 groups:
    a. Small crescent – a crescent involving 10 to 50% of the glomerular circumference
    b. Medium crescent - a crescent involving 50 to 80% of the glomerular circumference
    c. Large crescent - crescent involving more than 80% of the glomerular circumference
4. Crescents will be categorised as cellular, fibrocellular or fibrous as per the World Health Organization classification of renal disease.
5. The interval between disease onset and start of treatment will be reviewed under the following time periods
    a. Less than 1 month
    b. 1 to 3 months
    c. More than 3 months
6. Signs and symptoms will be defined as:
    a. Hypertension

       Systolic and/or diastolic blood pressure that is greater than the 95^{th} percentile for age, gender and height based on the Paediatric Task Force recommendations (13)
    b. Proteinuria

As evaluated by urine dipstick estimation, or by 24 hour quantitative measurement, or both (6)

c. Haematuria

As evaluated by urine dipstick estimation, or if visible with the naked eye (6)

d. Oliguria

Urine output that is less than 1 mL/kg/h in infants, or less than 0.5 mL/kg/h in children (14)

e. Glomerular Filtration Rate (GFR)

Calculated from the Schwartz estimate (15, 16)

$$GFR\ (ml/m/1.73m^2) = (k \times height) / serum\ creatinine$$

Where k = 0.33 for age less than 1 year and low birth weight <2500g

k = 0.45 for age less than 1 year and birth weight >2500g

k = 0.55 for a child or an adolescent female

k = 0.70 for an adolescent male

GFR is classified as normal if ≥90, mild reduction is between 60 to 89, moderate reduction is between 30 to 59, or severe reduction if <29 (17)

7. End stage kidney disease (ESKD) is defined as chronic kidney disease stage 5 (17)
8. Serum concentrations of urea, creatinine, albumin, C3, C4, antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA), antistreptolysin-O titre (ASOT), anti-glomerular basement membrane protein and human immunodeficiency virus (HIV) as per National Health Laboratory Service techniques.
9. Epidemiological and clinical findings will be evaluated and summarised in a table form. The following parameters will be considered:
    a. Age
    b. Gender
    c. Duration of symptoms at presentation
    d. Signs and symptoms at presentation:
        i. Fever
        ii. Oedema
        iii. Oliguria
        iv. Hypertension

v. Haematuria
vi. Proteinuria
vii. Others

e. Dialysis
f. Treatment given and outcome in relation to proteinuria and renal function
g. Blood results:
    i. Serum creatinine level at admission, peak serum creatinine, serum creatinine at follow – up
    ii. Protein and albumin levels
    iii. C3, C4
    iv. ANA, ANCA
    v. ASOT titre
    vi. Anti – glomerular basement membrane protein
    vii. HIV
    viii. Urine dipsticks and urine microscopy, culture and sensitivity (MC+S)
    ix. Urine protein : creatinine ratio

10. Renal biopsy specimen findings will be reported as per technique used: light microscopy, immunofluorescence or electron microscopy. Findings will be summarised in a table form regarding the following histopathological features:
    i. Total number of glomeruli in a biopsy specimen
    ii. Percentage of glomeruli with crescentic involvement
    iii. Type of crescents
    iv. Partial or circumferential involvement
11. Presenting signs and symptoms will be subdivided into the type of crescents and percentage of glomeruli affected on renal biopsy.
12. Treatment modalities will be reviewed.

Data statistics

The Fisher's exact test will be used to assess:

1. Symptoms and progression to ESKD

2. Treatment modalities and progression to ESKD
3. Type of crescents and progression to ESKD
4. Percentage of crescents and progression to ESKD

95% confidence intervals for parameters of interest will be reported, and p-values of <0.05 will be considered statistically significant.

Limits

Files may not be available and data may be missing from files, these patients may be excluded from the study.

Protection of human research participants

This study is retrospective; therefore there are no risks to participants. Participants in the study will be identified for study purposes with a unique study number. Participants will incur no extra costs based on participation in the study. No additional study-specific visits are required.

Review board approval

The protocol and consent forms have been approved by the Human Research Ethics committee (HREC), University of the Witwatersrand. The clearance certificate number is M121160.

Summary of results will be reported to the HREC on completion of the study. Results may be presented at professional clinical meetings and national or international scientific meetings. Results will be submitted for publication in a peer-reviewed journal.

Time frames for study conduct

HREC submission date: 7 November 2012

Recruitment of subjects: Retrospective

Funding: Due to being a retrospective, patient-record review, there are no study-specific costs associated with the study.

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Appendix A

Data collection sheet

Patient study number ☐

Age ☐

Gender ☐

Symptoms at presentation

Oliguria ☐ Yes ☐ No

Oedema ☐ Yes ☐ No

Macroscopic haematuria ☐ Yes ☐ No

Other ☐ Yes ☐ No ☐

Signs at presentation

Hypertension ☐ Yes ☐ No

Microscopic haematuria ☐ Yes ☐ No

Proteinuria ☐ Yes ☐ No

Other ☐ Yes ☐ No ☐

Duration of symptoms at presentation ☐

Blood results at presentation

Urea ☐ Yes ☐ No Result ☐

☐

Creatinine	☐ Yes	☐ No	Result	
Albumin	☐ Yes	☐ No	Result	
C3	☐ Yes	☐ No	Result	
C4	☐ Yes	☐ No	Result	
ANA	☐ Yes	☐ No	Result	
ANCA	☐ Yes	☐ No	Result	
ASOT	☐ Yes	☐ No	Result	
Anti-GBM protein	☐ Yes	☐ No	Result	
HIV	☐ Yes	☐ No	Result	

<u>Glomerular filtration rate at presentation</u>

k

Length

Creatinine

GFR

Normal (≥90)	☐ Yes	☐ No
Mild reduction (60-89)	☐ Yes	☐ No
Moderate reduction (30-59)	☐ Yes	☐ No
Severe reduction (<29)	☐ Yes	☐ No
Kidney failure (<15 or dialysis)	☐ Yes	☐ No

<u>Interval between disease onset and start of treatment</u>

Less than one month	☐ Yes	☐ No

One-three months ☐ Yes ☐ No

More than three months ☐ Yes ☐ No

Renal biopsy techniques

Light microscopy ☐ Yes ☐ No

Electron microscopy ☐ Yes ☐ No

Immunofluorescence ☐ Yes ☐ No

Renal biopsy findings

Small crescents (10-50%) ☐ Yes ☐ No

Medium crescents (50-80%) ☐ Yes ☐ No

Large crescents (>80%) ☐ Yes ☐ No

Cellular crescents ☐ Yes ☐ No

Fibrocellular crescents ☐ Yes ☐ No

Fibrous crescents ☐ Yes ☐ No

Treatment

Immunosuppressants ☐ Yes ☐ No

Type ☐

Anti-platelet drugs ☐ Yes ☐ No

Plasma exchange ☐ Yes ☐ No

Dialysis ☐ Yes ☐ No

Supportive ☐ Yes ☐ No

Follow-up

Date of last follow-up ☐

Signs at follow-up

Hypertension	☐ Yes	☐ No
Microscopic haematuria	☐ Yes	☐ No
Proteinuria	☐ Yes	☐ No
Other	☐ Yes	☐ No

Blood results at follow-up

Urea	☐ Yes	☐ No	Result ☐
Creatinine	☐ Yes	☐ No	Result ☐
Albumin	☐ Yes	☐ No	Result ☐
C3	☐ Yes	☐ No	Result ☐
C4	☐ Yes	☐ No	Result ☐
ANA	☐ Yes	☐ No	Result ☐
ANCA	☐ Yes	☐ No	Result ☐
ASOT	☐ Yes	☐ No	Result ☐
Anti-GBM protein	☐ Yes	☐ No	Result ☐
HIV	☐ Yes	☐ No	Result ☐

Glomerular filtration rate at presentation

k ☐

Length ☐

☐

☐

Creatinine

GFR

Normal (≥90)	☐ Yes	☐ No
Mild reduction (60-89)	☐ Yes	☐ No
Moderate reduction (30-59)	☐ Yes	☐ No
Severe reduction (<29)	☐ Yes	☐ No
Kidney failure (<15 or dialysis)	☐ Yes	☐ No

Patient review at 30 June 2012

Alive and well	☐ Yes	☐ No
Alive and with ESKD	☐ Yes	☐ No
Demised	☐ Yes	☐ No

Appendix D – Turn-it-in report

684781:CGNturnitin.docx

by Sajeda Mansoor

Dr KL Petersen
MBBCh, DCH, DTM&H, FCPaed.
MMed, Cert Neph (Paed)
MP 0436887

Submission date: 21-Apr-2020 10:08PM (UTC+0200)
Submission ID: 1303926687
File name: ssignments_f307a098-5afe-4340-a275-5d2c13581106_CGNturnitin.docx (3.79M)
Word count: 5707
Character count: 31018

Appendix E - South African Medical Jounal Author Guidelines
http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings

- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.