

Study of paediatric renal biopsies with clinicopathologic correlation and comparison with literature on adult renal biopsies

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Abstract

Introduction: Renal biopsy is frequently used in complete work-up for renal diseases. The kidney reacts in a limited number of patterns to various injuries and the clinical manifestations corresponding to these reactions are also limited.

Aim of the study: To study the non-neoplastic renal diseases in paediatric population 0-15 year age, to study the differences in the disease prevalence between paediatric and adult population, and to document the geographic variation in renal diseases.

Materials and Methods: The renal biopsies from 0-15 year age group of both genders were studied for light microscopy and immunofluorescence studies. The clinical presentation of the patients such as nephrotic or nephritic or both or as acute renal failure was noted for clinic pathologic correlation. The paediatric renal diseases were compared with adult renal diseases based on literature search. Also the geographic variations were studied and compared based on published data from different countries.

Results: Nephrotic syndrome was the most common clinical presentation for paediatric renal diseases. Minimal change disease (37.8 %) and FSGS (22.4 %) cases commonly presented as nephrotic syndrome. PIGN (37.6 % cases) presented frequently as nephritic syndrome in the paediatric age group.

Conclusion: Nephrotic syndrome is the most common indication for renal biopsy and minimal change disease is the commonest cause of nephrotic syndrome in children. Incidence of membranous nephropathy and IgA nephropathy is relatively less in India. PIGN is the most common cause of acute renal failure in the paediatric age group. In systemic lupus erythematosus, most common presentation is nephrotic syndrome with class IV lupus nephritis being more frequent.

Keywords: Acute renal failure, IgA nephropathy, Nephrotic syndrome, Nephritic syndrome, Paediatric age group, Renal biopsy.

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Introduction

Renal biopsy is an invaluable method used in evaluation of renal diseases. The kidney reacts in a limited number of ways to various injuries and the clinical manifestations corresponding to these reactions are also limited.¹ Spectrum of renal diseases in children is different from adults and a geographic variation also exists. Renal diseases are not uncommon in paediatric age group and their diagnosis is important for treatment and prognosis. Histopathological examination of renal biopsies in a patient with renal disease forms an important part of clinical workup. Along with routine histopathology, immunofluorescence studies are also required in most of the cases and electron microscopy is required in some cases to arrive at a specific diagnosis. The spectrum of renal diseases in developing countries is different from that in developed countries.²

Aims and Objectives

To document the various non-neoplastic lesions in paediatric age group.

To compare the prevalence of diseases in age-groups of 0-5, 6-10 and 11-15 years in our study population.

To correlate clinical findings with histopathology and immunofluorescence results.

To study the differences in the disease prevalence between paediatric and adult population based on literature search.

To document the geographic variation in renal diseases.

Materials and Methods

This was a retrospective and prospective study carried out in the department of Pathology, Apollo Hospitals, Jubilee Hills, Hyderabad, over a period of twelve years. Only paediatric renal biopsies in age 0-15 year age group received

during this period were considered. A total of 958 renal biopsies were received out of which 64 (6.6 %) were inadequate and 95 cases required further extensive studies like electron microscopy and hence, were excluded. So only 799 cases with a definite diagnosis made on light microscopy and immunofluorescence or only light microscopy were included in the study.

Inclusion criteria: Renal biopsies only from paediatric age group 0-15 years were considered.

Exclusion criteria: Inadequate renal biopsies, Biopsies requiring electron microscopy.

Renal biopsies were performed by clinicians. A cutting needle through percutaneous route was used. Two cores were preferred from each case. One core was taken for light microscopy and the other was processed for immunofluorescence study. The biopsies were transported to the laboratory immediately without any delay. The biopsies for light microscopy were fixed in Bouin's fluid and for immunofluorescence the material was received in gauze soaked in cold saline. Michel's transport medium was used if delay more than a few hours was expected. For light microscopy the tissue was fixed for 6 hours in Bouin's fluid followed by overnight fixation in 10 % neutral buffered formalin and then submitted to a short processing. Biopsy cores were serially sectioned and 5 to 6 sections were placed on each slide. Two slides each were attained for hematoxylin and eosin, trichrome and silver methenamine stain. Other stains like Congo red, Verhoff stain were done wherever indicated.

The renal biopsies containing 5 to 10 glomeruli were considered adequate.

The microscopic examination included assessment of glomeruli for: Size, cellularity,

segmental or global changes, mesangium, leukocytes, capillary walls, necrosis, thrombi, adhesions to Bowman's capsule, deposits with type and location, crescents with type and percentage, sclerosis with distribution and percentage.

The tubules were examined for: Necrosis, reparative changes, dilatation, casts, cellular inclusions, vacuolization and basement membrane changes.

The blood vessels were examined for: Intimal thickening, elastic changes, hyalinosis, thrombosis, embolism, necrosis, inflammation and juxtaglomerular apparatus.

The interstitium was examined for: Edema, inflammation, type of inflammatory cells and fibrosis.

For immunofluorescence: The positive or negative reactions along with specific components were noted. The pattern of reaction i.e. linear or granular, the intensity and distribution of reaction were noted.

For immunofluorescent technique cryostat sections were taken at 2-5 micron thickness. Sections were dried at room temperature for 15 to 30 minutes. Anti IgG, IgM, IgA, C3c, C1q, fibrinogen, Kappa and Lambda light chains were used. After the light microscopic and immunofluorescent evaluation of the renal biopsies the study was further analyzed in 91 cases with a clinical follow-up for progression of the disease. The findings in this study were compared with other studies. A comparison of incidence of diseases between different groups was performed. A comparison of our findings with adult and elderly population was done. A comparison of the results with same age group in developed and developing countries was done.

Results

Table 1: Distribution of cases based on clinical presentation and biopsy reports

Histopathology and Immunofluorescence	Clinical presentation			
	Nephrotic syndrome No. of cases (%)	Nephritic syndrome No. of cases (%)	Nephrotic-Nephritic syndrome No. of cases (%)	Acute renal failure No. of cases (%)
MCD	196 (37.8%)			
FSGS	116 (22.4 %)	5 (3.6%)	6 (16.6%)	
Mild DMP	68 (13.1%)	8 (5.8%)	3 (8.3%)	
Membranous nephropathy	30 (5.8 %)	2 (1.4%)	2 (5.5%)	1 (0.9%)
MPGN	23 (4.4 %)	4 (2.9%)	7 (19.4%)	1 (0.9%)
Mesangioproliferative GN	21 (4.0 %)	3 (2.2%)	4 (11.1%)	5 (4.6%)
DPGN with PIGN	14 (2.7 %)	52 (37.6%)	7 (19.4%)	15 (14.0%)
IgA nephropathy	5 (0.9 %)	14 (10.1%)	1 (2.8%)	3 (2.8%)
Lupus nephritis	18 (3.4 %)	16 (11.6%)	2 (5.5%)	1 (0.9%)

Alport's	2 (0.3 %)			
Congenital Nephrotic syndrome	5 (0.9 %)			1 (0.9%)
Congenital Nephrotic syndrome (Finnish type)	2 (0.3 %)			
Infantile Nephrotic syndrome	2 (0.3 %)			
Diffuse mesangial sclerosis	2 (0.3 %)			1 (0.9%)
Renal amyloidosis	2 (0.3 %)			
Sclerosing GN	2 (0.3 %)	2 (1.4%)		1 (0.9%)
Segmental necrotizing GN	2 (0.3 %)			1 (0.9%)
Chronic GN	2 (0.3 %)	1 (0.7%)		4 (3.7%)
End stage renal disease	1 (0.2 %)			
IgM nephropathy	1 (0.2 %)			
Vasculitis	2 (0.3 %)			2 (1.8%)
Tubulointerstitial nephritis	1 (0.2 %)	4 (2.9%)	1 (2.8%)	8 (7.4%)
C1q nephritis	2 (0.3 %)			
HSP		10 (7.2%)		
HUS		5 (3.6%)		5 (4.6%)
Crescentic GN		6 (4.3%)	3 (8.3%)	24 (23.0%)
Thin BMD		4 (2.9%)		
Amyloidosis		1 (0.7%)		1 (0.9%)
ATN				7 (6.5%)
Obstructive uropathy				1 (0.9%)
Fungal nephritis				1 (0.9%)
Chronic allograft nephropathy				1 (0.9%)
Malignant hypertension				1 (0.9%)
Acute cortical necrosis				7 (6.5%)
AR polycystic kidney				3 (2.8%)
Non-Hodgkin's Lymphoma				2 (1.8%)
Primary hyperoxalosis				2 (1.8%)
Total (799)	518 (100%)	138 (100%)	36 (100%)	107 (100%)

MCD: Minimal change disease, FSGS: Focal segmental glomerulosclerosis, DMP: Diffuse mesangial proliferation, MPGN: membranoproliferative glomerulonephritis, DPGN: Diffuse proliferative glomerulonephritis, PIGN: Post infectious glomerulonephritis, HUS: Hemolytic uremic syndrome, HSP: Henoch Schonlein purpura, BMD: Basement membrane disease, ATN: Acute tubular necrosis, AR: Autosomal recessive

Table 2: Distribution of cases according to age and gender

Biopsy findings (No. of cases)	Age	Male	Female	Total
MCD (196)	0-5	42	20	62
	6-10	48	28	76
	11-15	29	29	58
Mild diffuse mesangial proliferation (79)	0-5	12	06	18
	6-10	09	11	20
	11-15	21	20	41
FSGS (127)	0-5	08	09	17
	6-10	20	17	37
	11-15	40	33	73
Membranous glomerulonephritis (35)	0-5	02	01	03
	6-10	05	03	08
	11-15	12	11	24
Mesangioproliferative GN (28)	0-5	04	01	05

	6-10	01	02	03
	11-15	15	05	20
MPGN I (37)	0-5	01	02	03
	6-10	03	04	7
	11-15	16	11	27
MPGN II (4)	0-5	0	0	0
	6-10	0	0	0
	11-15	1	03	04
DPGN with PIGN (73)	0-5	01	04	05
	6-10	18	04	22
	11-15	20	26	46
HSP (10)	0-5	0	0	0
	6-10	2	0	2
	11-15	5	3	8
IgA nephropathy (23)	0-5	01	0	01
	6-10	02	02	04
	11-15	11	04	18
Lupus nephritis (37)	0-5	0	04	04
	6-10	0	03	03
	11-15	0	29	30

In lupus nephritis, the class-wise distribution was: Class 1 – 1 case, Class 2- 8 cases, Class 3 – 7 cases, Class 4 – 14 cases and class 5- 7 cases and Class 6- zero cases.

In Class 3; 4 cases showed mild to moderate activity with no chronicity and in Class 4; 2 cases showed significant activity with no chronicity and 12 cases showed mild to moderate activity with no chronicity.

In the MCD (196 cases), 33 and 36 cases, in mild diffuse mesangial proliferation 17 and 21 cases, in FSGS 11 and 30 cases, were steroid dependent and steroid resistant respectively.

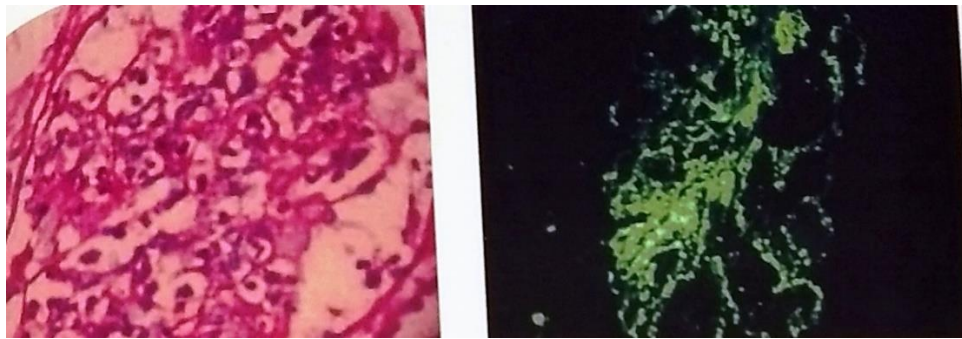


Fig. 1: Post infectious glomerulonephritis (PAS stain 400X and immunofluorescence C3c 400X)

Discussion

Table 3: Comparison of nephrotic syndrome in paediatric age group

Study	No. of cases	MCD %	FSGS %	MPGN %	Mesangio-proliferative GN %	Membranous nephropathy %
Kumar et al ³ (India)	290	32.0%	34.0%	15.0%	11.0%	2.0%
Simpson et al ⁴ (New Zealand)	157	37.0%	19.0%	23.0%	-	-
Al-Rasheed et al ⁵ (Saudi Arabia)	128	23.3%	24.0%	24.0%	-	-

Chen et al ⁶ (Taiwan)	347	17.8%	-	1.2%	26.9%	9.8%
Coppo et al ⁷ (Italkid)	432	11.6%	8.5%	5.5%	9.5%	5.0%
Ko et al ⁸ (Korea)	662	57.0%	21.0%	-	-	-
White et al ⁹ (Birmingham)	145	74.2%	9.3%	7.0%	5.4%	1.5%
Yahya et al ¹⁰ (UAE)	490	26.2%	15.4%	26.6%	-	28.3%
Absar et al ¹¹ (Pakistan)	41	37.0%	12.0%	10.0%	2.0%	7.0%
Present (India)	518	37.8%	22.4%	4.4%	3.0%	5.8%

In our study, 54% (518/958) of the individuals presented with nephrotic syndrome which was considerably less than the observations made by Ko et al,⁴ 67 %, Diouf et al^[12] at Senegal 67%, and McKinney et al^[13] in Yorkshire 88%.

As mentioned in Table 3, the prevalence of MCD in this study was 37.8% which is higher than the studies conducted by Kumar et al,³ Rasheed et al,⁵ Chen et al,⁶ Coppo et al,⁷ Yahya et al,¹⁰ and similar in studies by Simpson et al⁴ at 37% and Absar et al¹¹ at 37 %. However with the exception of the observation made by Ko et al⁴ and White et al⁹ who found higher frequency of MCD at 57% and 74.2 %. Our study as in other studies mentioned above shows that minimal change nephropathy is the commonest cause of a steroid resistant/dependent nephrotic syndrome in children.

The prevalence of FSGS in this study (22.4%) was similar to the studies conducted by Ko et al⁸ 21% and Rasheed et al⁵ 24% while it was significantly lower than the observation made by Kumar et al³ 38%. Observations made by Simpson et al⁴ 19%, Coppo et al⁷ 8.5%, White et al⁹ 9.38%, Yahya et al¹⁰ 15.4%, and Absar et al¹¹ 12% showed significantly lower frequency. In our study, 14 out of 127 patients had varying degree of renal insufficiency and this is as expected in FSGS.

Study conducted by Chen et al⁶ showed lower prevalence of MPGN (1.2%) in comparison to our study where it was 4.44%. Coppo et al⁷ observed 5.5%, White et al as 7.03%, Absar et al¹¹ 10%, Kumar et al³ 15%, Simpson et al⁴ 23%, Rasheed et al⁵ 24%, Yahya et al¹⁰ 26.6%, showed higher frequency of MPGN. Our figures seem to be between those in the West and studies from Africa, Jordan and Arabia.

The prevalence of mesangioproliferative glomerulonephritis in the present study was 3% and significantly lower than the studies of White et al⁹ 5.4%, Coppo et al⁷ 9.5%, Kumar et al³ 11%, Chen et al⁶ 26.9% and Hameed et al¹¹ 33.6%.

Membranous nephropathy (MN) had higher frequency in studies conducted by Chen et al 9.8%, Yahya et al¹⁰ 28.3%. In Taiwan, the membranous nephropathy was secondary to hepatitis B antigenemia and the prevalence was significantly lower in the studies conducted by Kumar et al³ at 2%, White et al⁹ 1.5%. In the present study MN was 5.8% cases, which is similar to the observation of Coppo et al⁷ of 5%. None of our patients were HIV or HBSAg positive or had any other findings to suggest secondary membranous glomerulonephritis.

The study conducted by Yap et al¹⁴ in Singapore found higher frequency of FSGS, mild diffuse mesangial proliferation, mesangioproliferative glomerulonephritis, membranous nephropathy, diffuse mesangial sclerosis and diffuse sclerosing glomerulonephritis while the prevalence of crescentic glomerulonephritis diffuse endocapillary glomerulonephritis were higher in this study.

Haas et al² in Chicago, USA had a higher frequency of thin basement membrane disease, Alport's disease, IgA nephropathy and MCD than the present study. Briganti et al¹⁵ in Australia had glomerular lupus, FSGS, IgA nephropathy and MCD as the common glomerular pathologies in children. Ko et al⁸ found higher prevalence of DPGN and PIGN with nephritic presentation.

The study done by Yap et al¹⁴ in Singapore showed lower prevalence of DPGN with PIGN.

Table 4: Comparison with adult nephrotic syndrome

Study	No. of cases	MCD	FSGS	Membranous	IgAN	Lupus	Mesangio-proliferative GN
Woo et al ¹⁶ (Singapore)	100	15.0%	-	5.0%	4.0%	13.0%	60.0%
Diouf et al ¹² (Dakar)	115	6.0%	47.0%	6.0%	5.0%	13.0%	1.0%
Haas et al ² (Chicago) Earlier decade/Later decade	-	23.0% -	15.0% / 35.0%	36.0% / 33.0%	-/-	-/-	-/-
Rychik et al ¹⁷ (Czech Republic)	4004	12.4%	-	-	34.5%	-	11.3%
Present (India)	518	37.8%	22.4%	5.8%	2.0%	3.7%	3.0%

As mentioned in Table 4, comparative analysis with the adult nephrotic syndrome revealed: MCD in this study was 37.8 % which is less than in adults as expected. Mesangioproliferative glomerulonephritis presents as nephrotic syndrome more commonly in adults.

The incidence of IgA nephropathy in this study is far less than in other studies.

Briganti et al¹⁵ in Australia found the common glomerulonephritis in adults in order of frequency were IgA nephropathy, FSGS, lupus and vasculitis.

Lai et al¹⁸ in Hong Kong conducted a study on 961 adult cases and showed MCD as the most common cause of NS which was similar to our study. The frequency of MPGN, FSGS and MN were similar to this study. MN was associated with hepatitis B antigenemia. Prevalence of IgA nephropathy was higher in other studies^{2,12,16,17} as compared to our study.

Comparison with nephrotic syndrome in elderly: Moulin et al¹⁸ have observed 31.8% MCD, 27.2% membranous nephropathy and 22.7% amyloidosis in the elderly with nephrotic presentation. Kingswood et al¹⁹ have observed 4% and 33% cases of MCD and membranous nephropathy respectively with nephrotic presentation whereas, Haas et al have reported 16.8% cases and 9.6% of membranous nephropathy and amyloidosis presenting as nephrotic syndrome. Prevalence of MCD was higher in present study in paediatric age group. MN was more prevalent in other studies.^{2,19} Study by Haas et al² showed higher incidence of myeloma kidney and necrotizing vasculitis.

Table 5: Paediatric acute renal failure (ARF)

Diseases	Yoshiya et al ²⁰	Shah et al ²¹	Olowo et al ²²	Present study
HUS	35.5%	12.0%	5.5%	4.6%
TIN	21.1%	-	2.8%	4.6%
IgANephropathy	10.0%	-	-	2.8%
MPGN	8.9%	-	-	0.9%
Lupus	5.5%	-	-	0.9%
PIGN	4.4%	6.0%	-	14.0%
Acute cortical necrosis	1.1%	18.2%	-	3.7%
ATN	-	66.6%	-	6.4%
HSP	1.1%	-	-	-
ANCA GN	1.1%	-	-	-
Crescentic GN	-	6.0%	-	23.0%
Cortical	-	6.0%	-	2.8%

necrosis				
Burkitt's lymphoma	-	-	47.2%	-
Glomerulonephritis	-	-	27.8%	-

TIN: Tubulointerstitial nephritis, ANCA GN: Anti neutrophil cytoplasmic antibody GN

As mentioned in Table 5, Yoshiya et al²⁰ in Japan conducted a study on paediatric acute renal failure (ARF) which showed higher incidence of Hemolytic uremic syndrome, tubulointerstitial nephritis, IgA nephropathy, MPGN and lupus nephritis.

Study conducted by Shah et al²¹ in Bombay on Paediatric age group ARF had higher incidence of acute tubular necrosis, HUS, acute cortical necrosis, glomerulonephritis and patchy cortical necrosis. This study showed higher incidence of crescentic glomerulonephritis and PIGN.

Olowo et al²² found higher incidence of HUS and glomerulonephritis. Many of the cases with ARF were secondary to Burkitt's lymphoma. In our study there were a few additional causes for ARF such as autosomal recessive polycystic kidney disease, non-Hodgkin's lymphoma, mesangioproliferative glomerulonephritis, MN, primary hyperoxalosis, diffuse mesangial sclerosis, congenital NS, obstructive uropathy, fungal nephritis, segmental necrotizing glomerulonephritis, chronic allograft nephropathy, necrotizing vasculitis and amyloidosis.

Table 6: Comparison of paediatric ARF with adult ARF

	Kazi et al ²³ (Pakistan)	Prakash et al ²⁴ (India)	Present study (107)
ATN	38.6%	15.6%	6.4%
Acute cortical necrosis	22.7%	6.2%	3.7%
Chronic GN	31.0%	21.9%	23.0%
TIN	5.0%	15.6%	4.6%
Acute pyelonephritis	1.8%	-	-
PIGN	-	15.6%	14.0%
Necrotizing vasculitis	-	12.5%	0.9%
MPGN with crescents	-	6.2%	0.9%

As mentioned in Table 6, Kazi et al²³ in Pakistan found higher incidence of acute tubular necrosis, acute cortical necrosis, chronic glomerulonephritis and similar incidence of tubulointerstitial nephritis.

Prakash et al²⁴ from BHU, India found higher incidence of ATN (15.6%). Study done by Dagger et al²⁵ USA found lower incidence of FSGS leading to ARF.

A study conducted by Haas et al²⁶ showed higher incidence of crescentic glomerulonephritis (31.2%) acute tubulointerstitial nephritis (18.6%), ATN (14.2%), Anti GBM nephropathy (4%) leading to renal failure in elderly population above 60 years.

Prevalence of IgA nephropathy (3.6%) was similar to present study. Other conditions like atheroemboli, light chain cast nephropathy and benign nephrosclerosis which they encountered

were not seen in paediatric age group in our study.

Study conducted by Kari et al²⁷ in UAE found MPGN presented in earlier age groups whereas in our study it was observed in later age groups.

Utsumomiya et al²⁸ in Japanese children and Johnson et al²⁹ (in Leed) in adults found higher incidence of IgA nephropathy. For school children in Japan, routine urine analysis screening is mandatory which possibly explains the higher detection rate for IgA nephropathy in Japan.³⁰

Conclusion

Nephrotic syndrome is the most common indication for renal biopsy and minimal change disease is the commonest cause of nephrotic syndrome in children. Incidence of membranous nephropathy is lower in India as compared to

East Asian and African countries. IgA nephropathy is relatively less prevalent as compared to Western countries. Mild mesangial proliferation is the most common morphology seen in IgA nephropathy. PIGN is the most common cause, whereas, HUS is an uncommon cause of acute renal failure in the paediatric age group. In systemic lupus erythematosus, most common presentation is nephrotic syndrome with class IV lupus nephritis being more frequent. The causes for paediatric ARF are different from causes of adult ARF as observed on literature search. Though light microscopy and immunofluorescence are mandatory for evaluation of renal diseases, they have their own limitations and there are many renal lesions which specifically require electron microscopy for definite diagnosis.

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