Morphological Patterns of Glomerular Diseases among Children Studied by Light and Immunofluorescence Microscopy at Selected Tertiary Care Hospitals

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Abstract

Background: Glomerular disorders constitute one of the major causes of morbidity and mortality in children and adult population. Diagnosing the pattern of glomerular diseases is important as the treatment and outcome differs in different types. This study was undertaken to find out the various morphological patterns of glomerular diseases among children at selected tertiary care hospital in Bangladesh.

Methods: This cross-sectional study was carried out at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from the period of September 2014 to June 2016. Renal biopsy samples of children with nephrotic syndrome and nephritic syndrome, children having asymptomatic haematuria and isolated proteinuria and children presenting with acute and chronic renal failure were included in this study. For routine histopathological examination, tissue was preserved in 10% formalin. After completion of routine paraffin processing, hematoxylin and eosin (H&E) and periodic acid Schiff (PAS) staining were done. For direct immunoflurescence study, tissue was preserved in normal saline and processed according to standard protocol of immunoflurescence study. Routine H&E and PAS stained sections of the renal biopsy samples were examined for changes in glomeruli, tubules, interstitium and blood vessels. The site, pattern and degree of antibody deposition in the renal tissue were observed by immunoflurescence study. Final diagnosis was made by correlation of histopathological, immunofluorescence and clinical findings.

Results: Mesangial proliferative glomerulonephritis (MesPGN) was the most common primary glomerular disease diagnosed in patients followed by minimal change disease, IgA nephropathy, membrano-proliferative glomerulonephritis and crescentic glomerulonephritis. Lupus nephritis was the most common secondary glomerular disease diagnosed in patients.

Conclusion*:* The reported prevalence of different morphological patterns of glomerular diseases among children in Bangladesh seems to be no definite pattern. In fact, the patterns vary according to the geographical area, environment and racial background.

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Keywords: Glomerular diseases among children, Light and immunoflurescence microscopy, Tertiary care hospitals.

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Introduction

Glomerular disease indicates initial and major point of insult within the glomerulus of renal tissue.[1] The clinical presentation may vary from patient to patient. On the other hand, same clinical presentation may be associated with many glomerular diseases. The prevalence of glomerular diseases is different according to the geographic area, race and age.[1] Studies have shown a changing pattern of glomerular diseases.[2] Systemic lupus erythematosus (SLE) nephritis and membranoproliferative glomerulonephritis (MPGN) were the most frequent glomerular diseases in children in Nepal.[3] Minimal change disease (MCD) was the most common form of glomerular diseases in children in Iran.[4,5] Acute glomerulonephritis (AGN), Henoch-Schoeniein purpura nephritis (HSPN) and mesangial proliferative glomerulonephritis (MesPGN) are also common in children.[1]

A number of different diseases can result in glomerular disease. It may be the direct result of an infection or a nephrotoxic drug, or may result from a systemic disease, like diabetes or systemic lupus erythematosus and also may be idiopathic.[1] Accurate diagnosis of glomerular diseases requires renal biopsy and histopathological examination by light microscopy, immunofluorescence study and electron microscopy. In addition, it requires correlating clinical features and biochemical parameters with histopathology results. Facilities for electron microscopy are not readily available in most centers. In most cases, light microscopy and immunofluorescence studies are satisfactory for the definitive diagnosis of glomerular diseases. For example, in early stages of membranous nephropathy there is no thickening of the glomerular basement membrane (GBM) and no spikes on silver stain, and so it may not be distinguished from minimal change disease by light microscopy.[1] Immunofluorescence study reveals the fine granular deposition of immunoglobulin and complement and confirms the diagnosis of membranous nephropathy. At the same time, distinguishing it from anti-GBM nephritis where liner deposits are seen in immunofluorescence study.[1] Immunofluorescence microscopy provides insight into the pathogenesis of glomerular diseases and it is very useful in diagnosing primary renal diseases and assessing the nature and severity of renal involvement in various systemic disorders.

The epidemiology of biopsy-confirmed renal disease provides useful information about the prevalence of the renal disease and its clinical manifestations. The epidemiology of glomerular diseases follows racial and geographical distributions that are influenced by a higher overall prevalence of infectious diseases and differences in social and economic status.[6] The present study was done to find out the different morphological patterns of glomerular diseases among children at selected tertiary care hospitals in Bangladesh.

Methods

This was a cross sectional study carried out at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during the period of September 2014 to June 2016. A total of 135 renal biopsy samples collected from children under 14 years of age admitted at the Department of Pediatric Nephrology BSMMU, Dhaka and the Department of Pediatric Nephrology Dhaka Shishu (Children) Hospital were enrolled in this study. Renal biopsy samples of children with nephrotic syndrome and nephritic syndrome, children having asymptomatic haematuria and isolated proteinuria and children presenting with acute

and chronic renal failure were included in this study. Patients aged above 14 years, renal biopsy samples with inadequate glomeruli and children presented with obstructive uropathy were excluded from the study. Clinical data were collected with special attention to patient's age, sex, clinical presentation, results of laboratory investigation and were recorded in a pre-designed proforma.

Two samples of renal tissue were obtained from each patient by percutaneous needle biopsy performed by experienced nephrologists after explaining the procedure to the legal guardian of the patients and taken their written consent. Specimens for light microscopy were preserved in 10% formalin. Those for immunofluorescence study, was collected in normal saline and stored in deep freezer for subsequent cryostat sectioning.

Tissue in 10% formalin was processed routinely and embedded in liquid paraffin. Then sections were cut and stained with Haematoxyllin and eosin (H&E) and periodic acid schiff (PAS) stains. Routine H&E and PAS stained sections of the renal biopsy samples were examined for changes in four components: glomeruli, tubules, interstitium and blood vessels. The glomeruli were checked for cellularity, mesangium, basement membrane changes, segmental or global sclerosis, crescents, inflammatory cells, necrosis, thrombi, adhesion to Bowman's capsule and deposits. Epithelial changes and presence of various types of casts in tubules, interstitial inflammation and fibrosis, and changes in the blood vessels were also noted.

Tissue stored in freezer was transferred to the cryostat cabinet, placed on a holder, embedded in Optimal Cutting Temperature (OCT) compound and quickly frozen at -20^{o}C. Sections were cut in a -20^{o}C cooled chamber at a thickness of 4-5 micrometer and picked up on to specially designed ring slides. The sections were air dried, incubated and stained with properly diluted fluoresce in isothiocyanate (FITC) conjugated rabbit polyclonal anti human IgG, IgA, IgM, complement component 3 (C3), fibrinogen and complement component 1q (C1q). The slides were examined under fluorescence microscope. The site and pattern of antibody deposition were recorded. The degree of fluorescence (intensity) was graded as trace, (+), (++), (+++) and (++++). Histopathological, immunofluorescence and clinical findings were correlated prior to the final diagnosis. All data regarding patients were recorded methodically in a data sheet. Statistical analyses were carried out by SPSS-15. The results were presented in tables, figures, diagrams.

Result

It was observed that, majority (45.2%) of the patients belonged to age group more than 10 years. The mean age was found 8.7±3.96 years with range from 0.5 to 14 years. Majority (54.8%) were female. Male-female ratio was 1:1.2. Most common clinical presentation was nephrotic syndrome followed by systemic lupus erythematosus (SLE), nephritic syndrome, asymptomatic haematuria, Henoch-Schonlein purpura (HSP) nephritis, rapidly progressive glomerulonephritis (RPGN), infantile nephrotic syndrome, acute kidney injury (AKI) and isolated proteinuria (Table I). Mesangial proliferative glomerulonephritis (MesPGN) was the most common primary glomerular disease followed by minimal change disease, IgA nephropathy, membrano-proliferative glomerulonephritis 6(4.5%) and crescentic glomerulonephritis 4(2.9%). Lupus nephritis was the most common secondary glomerular disease diagnosed in 33(24.4%) patients (1: 2).

Table I: Distribution of the study participants by clinical presentation (n=135)

Clinical presentation	Number of patients	Percentage
Nephrotic syndrome	58	42.9
SLE	28	20.8
Nephritic syndrome	16	11.9
Asymptomatic haematuria	10	7.4
HSP nephritis	10	7.4
RPGN	6	4.4
Infantile nephrotic syndrome	3	2.2
AKI	3	2.2
Isolated proteinuria	1	0.7

SLE: Systemic lupus erythematosus, RPGN: rapidly progressive glomerulonephritis, HSP nephritis: Henoch-Schonlein purpura nephritis, AKI: acute kidney injury.

Table II: Distribution of the study participants by diagnosis (n=135)

Diagnosis	Number of patients	Percentage
Primary Glomerular Diseases:		
Mesangial proliferative GN (MesPGN)	43	31.9
Minimal change disease (MCD)	21	15.6
IgA Nephropathy	10	7.4
Membrano-proliferative GN (MPGN)	6	4.5
Crescentic glomerulonephritis	4	2.9
Acute post infectious glomerulonephritis	3	2.2
Diffuse proliferative glomerulonephritis	2	1.5
Focal segmental glomerulosclerosis (FSGS)	1	0.7
Membranous nephropathy	1	0.7
Chronic glomerulonephritis	1	0.7
Secondary Glomerular Diseases:		
Lupus nephritis	33	24.4
Henoch-Schonlein purpura nephritis	10	7.4

Table III: Immunofluorescence findings of the study patients

Diagnosis:	IgG	IgM	IgA	C3	C1q	Fibrin
Primary Glomerular Diseases:						
MesPGN (n=43)	7	38	5	16	3	0
MCD (n=21)	1	11	0	0	0	0
IgAN (n=10)	4	8	10	7	0	0
MPGN (n=6)	5	4	2	6	1	0
CrGN (n=4)	2	3	0	4	1	2
PSGN (n=3)	1	1	0	3	0	0
DPGN (n=2)	0	1	0	2	0	0
FSGS (n=1)	0	1	0	1	0	0
MN (n=1)	1	4	0	1	0	0
CGN (n=1)	0	1	0	1	0	0
Secondary Glomerular Diseases:						
LN (n=33)	25	30	19	28	22	0
HSPN(n=10)	3	8	10	5	0	0

Table IV: Correlation of clinical presentation with diagnosis

Clinical presentation	Primary glomerular diseases										Secondary Glomerular Diseases	
	MesPGN (n=43)	MCD (n=21)	IgAN (n=10)	MPGN (n=6)	CrGN (n=4)	PSGN (n=3)	DPGN (n=2)	FSGS (n=1)	MN (n=1)	CGN (n=1)	LN (n=33)	HSPN (n=10)
Nephrotic syndrome(n=58)	26	18	3	4	1	1	0	1	1	0	3	0
SLE (n=28)	0	0	0	0	0	0	0	0	0	0	28	0
Nephritic syndrome (n=16)	7	1	3	2	0	1	1	0	0	0	1	0
Asymptomatic haematuria (n=10)	7	0	2	0	0	0	0	0	0	0	0	1
HSP nephritis (n=10)	0	0	0	0	0	1	0	0	0	0	0	9
RPGN (n=6)	0	0	1	0	3	0	1	0	0	0	1	0
Infantile nephro-tic syndr. (n= 3)	1	2	0	0	0	0	0	0	0	0	0	0
AKI (n= 3)	1	0	1	0	0	0	0	0	0	1	0	0
Isolated protei-nuria ((n=1)	1	0	0	0	0	0	0	0	0	0	0	0

MesPGN: mesangial proliferative glomerulonephritis, IgAN: IgA nephropathy, MCD: minimal change disease, CrGN: crescentic glomerulonephritis, MPGN: membranoproliferative glomerulonephritis, PSGN: post streptococcal glomerulonephritis, DPGN: diffuse proliferative glomerulonephritis, FSGS: focal segmental glomerulosclerosis MN: membranous nephropathy, CGN: chronic glomerulonephritis, LN: lupus nephritis, SLE: systemic lupus erythematosus, RPGN: rapidly progressive glomerulonephritis, HSPN: Henoch-Schonlein purpura nephritis, AKI: acute kidney injury.

Table V: Comparison by diagnosis in various studies in children

Study	Country	MesPGN	MCD	IgAN	MPGN	RPGN	PSGN	DPGN	FSGS	MN	LN	HSPN
Present study (n=135)	Bangladesh	43 31.9%	21 15.6%	10 7.4%	6 4.5%	4 2.9%	3 2.2%	2 1.5%	1 0.7%	1 0.7%	33 24.4%	10 7.4%
Shrestha et al. (n=27)	Nepal	-	4 14.8%	-	8 29.6%	-	-	-	4 14.8%		8 29.6%	2 7.4%
Bhimma et al. (n=545)	South Africa	-	233 42.7%	-	21 3.8%	-	-	18 3.3%	136 25%	26 4.8%	-	-
Srivasta et al. (n=148)	USA	-	78 52.7%	-	14 9.5%	-	-	18 12.5%	34 23%	3 1.9%	-	-
Madani et al. (n=330)	Iran	-	90 27.2%	2 0.6%	23 7%	2 0.6%	-	24 7.2%	84 25.5%	19 5.7%	15 4.6%	1 0.3%

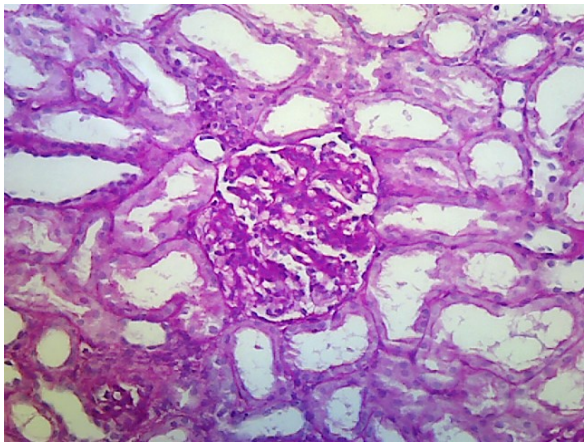

Figure 1. Photomicrograph of mesangial proliferative glomerulonephritis (PAS, x200, case no. 123).

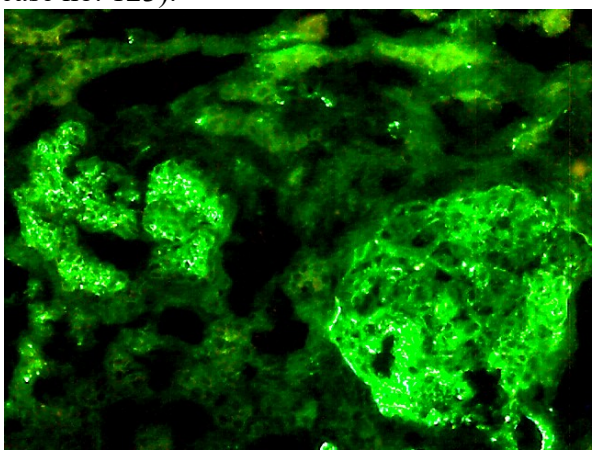

Figure 2. Photomicrograph of mesangial proliferative glomerulonephritis showing granular deposition of C3 (trace) in the mesangium (DIF, x200, case no. 123)

Discussion

Glomerular diseases constitute one of the major causes of morbidity and mortality in children and adult population. Diagnosing the pattern of glomerular diseases is important because the outcome and treatment differ in different types. Since glomerulonephritides are immunologically mediated, immunofluorescence microscopy is helpful in their diagnosis. Yet, combined analysis of light microscopy and immunofluorescence findings together with correlation of clinical features is essential for accurate diagnosis.

This cross sectional study was conducted with an aim to assess the clinical presentation of different types of glomerular diseases in children and to study the various histopathological changes in renal biopsy specimen of children. A total of 135 renal biopsy samples of the children with nephrotic syndrome, nephritic syndrome, asymptomatic haematuria, isolated proteinuria, and acute and chronic renal failure were enrolled in this study. Patients aged above 14 years, renal biopsy samples with inadequate glomeruli and children presented with obstructive uropathy were excluded from the study.

In this current study, it is observed that majority 61(45.2%) patients belonged to age group more than 10 years and the mean age was found 8.7±3.96 years with a range from 0.5 to 14 years. Similarly, Jahanzad et al. (2010) found the average patient age was 7.6 years; the range was between 2 and 15 years.[7] Shrestha et al. (2009) assessed the clinical features and histopathological diagnoses in renal biopsy specimens in children.[3] The mean age in this study was 9.7 years. Ali et al. (2012) found the mean age at the time of diagnosis was 6±2.1 years with a range from 1 month-18 years.[8] Almost eighty percent (78.7%) patients were below 10 years and 24.4% above 10 years of age in their study. Abdelraheem et al. (2010) found that the mean age at the time of presentation was 8.7 years with range from 2 months-16 years, which are comparable with the current study.[9]

In this present study, it was observed that majority 74(54.8%) patients were female and 61(45.2%) patients were male. Male-female ratio was 1:1.2. Shrestha et al. (2009)[3] found male to female ratio as 1:2. In another study, Ali et al. (2012) found male to female ratio as 2.3:1.[8] In study done by Abdelraheem et al. (2010), 60.2% children were male, which differ with the current study.[9]

Regarding the clinical presentation of the study patients, it was observed that more than one third (42.9%) patients had nephrotic syndrome followed by systemic lupus erythematosus 28(20.8%), nephritic syndrome 16(11.9%), haematuria 10(7.4%), Henoch-Schonlein purpura nephritis 10(7.4%), rapidly progressive glomerulonephritis 6(4.4), infantile nephrotic syndrome 3(2.2%), acute kidney injury 3(2.2%) and isolated proteinuria 1(0.7%) (Table I).

Nephrotic syndrome was the predominant (75.9%) clinical presentation in study by Al-Saegh & Assad (2013).[10] In another study Habib & Badruddoza (2012) found that the most frequent clinical presentation was nephrotic syndrome (67.37%) followed by nephritic syndrome (15.79%) and hematuria (8.42%).[11] Shrestha et al. (2009) found that the most frequent clinical presentation in the study group was nephrotic syndrome followed by haematuria and nephritic syndrome.[3] Similar observations regarding the clinical presentations were also observed by Abdelraheem et al. (2010), Muzaffar et al. (2003) and Iqbal et al. (1994).[9,12]

In this study, mesangial proliferative glomerulonephritis (MesPGN) was the commonest pattern of primary glomerular diseases (31.9%). Out of forty-three patients diagnosed as mesangial proliferative glomerulonephritis (MesPGN), twenty-five patients presented with nephrotic syndrome and IgM was the most frequent immune deposition (Table II, III). Earlier, a large international series, the International Study of Kidney Diseases in Children (ISKDC) have shown that, minimal change disease (MCD) is the most common type of glomerular disease in children. In the current study, minimal change disease was diagnosed in 21 (15.6%) patients. This may be due to the fact that, in our country, most children with minimal change disease are seen in general pediatric hospitals or in clinics and renal biopsies are not performed in majority of the cases. Moreover, diagnosis of minimal change disease is usually made by the absence of glomerular alteration in light microscopy and lack of immune deposits in immunofluorescence.[13] Minor degrees of mesangial matrix increment and/or hyper cellularity also form an integral part of minimal change disease.[14] When these features are more marked, it becomes difficult to segregate minimal change disease from mesangial proliferative glomerulonephritis.[15]

IgA nephropathy was noted in 10(7.4%) patients. The most frequent immune deposits were IgA (10 out of 10) and C3 (7 out of 10). A high prevalence of IgA nephropathy (47% and 45% of all primary glomerular diseases) has been reported from countries like Japan and China.[16] A prevalence of IgA nephropathy of 7–14% has been reported from South Asian countries such as India and Pakistan.[17,12] Membrano-proliferative glomerulonephritis (MPGN) was present in 6(4.5 %) of the cases. Four of these patients presented with nephrotic syndrome and C3 was the commonest immune deposition (six out of six) followed by IgG, which was present in five patients. Prevalence of membrano-proliferative glomerulonephritis (MPGN) was found 13.4% in Sudanese children.[9] It was 29.6% in children in Nepal.[3]

Crescentic glomerulonephritis was diagnosed in 4(2.9%) patients. Three of them presented with rapidly progressive glomerulonephritis (RPGN). Their most common immune deposition was C3 (four out of four) followed by IgM, which was present in three patient. Prevalence of crescentic glomerulonephritis was found 5.6% in Colombia.[18]

Acute post-infectious glomerulonephritis was seen in 3(2.2%) patients. It was secondary to streptococcal infection in the majority of

children. Reports from Saudi Arabia showed a low prevalence of post-infectious glomerulonephritis of 4%.[19] Higher prevalence has been reported from African countries. These may be due to increased incidence of various infectious diseases in African countries.

Diffuse proliferative glomerulonephritis was diagnosed in 2(1.5%) patients. It was found in 7.4% patient in Iranian children.[4]

Membranous nephropathy is uncommon in children. It was found in only one (0.7%) patient in this study. Percentage of focal segmental glomerulosclerosis (FSGS) was also low (0.7%). A higher frequency (21%) was reported from South African children.[20] Chronic glomerulonephritis was found only in one (0.7%) patient.

Lupus nephritis was the commonest secondary glomerular disease in our study seen in 33 (24.4 %) patients. It was also the commonest glomerular disease in Sudanese children.[9] In the current study, the commonest type of lupus nephritis was diffuse lupus nephritis (ISN/RPS class-IV), diagnosed in 15 patients. The next common type was mesangial proliferative lupus nephritis (ISN/RPS class-II) found in 13 patients. Membranous lupus nephritis (ISN/RPS class-V) was diagnosed in two patients. On immunofluorescence study, all the cases of lupus nephritis showed deposition of almost all the immunoglobins and complements. Recent studies have shown that, prevalence of lupus nephritis is increasing day by day both in adults and children.[2]

Henoch-Schonlein purpura (HSP) nephritis was diagnosed in 10(7.4%) patients. The clinical presentation of 9 patients out of 10 was Henoch-Schonlein purpura and their commonest immune deposition was IgA followed by IgM and C3. It was diagnosed in 7.4% patients in Nepal.[3]

Conclusion

From this study we found that most of the patients with glomerular disease belonged to age more than 10 years with slight female predominance. Nephrotic syndrome and systemic lupus erythematosus (SLE) were the commonest clinical presentations in patients with primary and secondary glomerular diseases respectively. Mesangial proliferative glomerulonephritis (MesPGN) was the most common primary glomerular disease and lupus nephritis was the most common secondary glomerular disease. The reported prevalence of different morphological patterns of glomerular diseases in children in Bangladesh seems to be no unique pattern.

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