

## Renal Histopathology in Childhood Nephrotic Syndrome at National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh– an experience of one decade

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### Abstract

**Background :** Nephrotic syndrome (NS) is one of the most common renal diseases in children. The cause of idiopathic nephrotic syndrome is still unknown. Once the prevalence of minimal change nephrotic syndrome occupied the three fourth portion of the total renal pathology and most of them were steroid sensitive. But list of steroid insensitive nephrotic syndrome become more longer today. Therefore renal biopsy is essential for histopathological diagnosis which guides the most accurate way for the treatment of such diseases.

**Objective :** The objective of this study was to find out the pattern of renal histopathology of selected cases of Idiopathic nephrotic syndrome.

**Materials and Method :** This prospective study was conducted from January 2004 to December 2015 among children who were suffering from nephrotic syndrome admitted in Paediatric nephrology department, National Institute of Kidney Diseases and Urology(NIKDU), Dhaka. Renal biopsy were done who fulfil the inclusion criteria. Obtaining ultrasound-guided percutaneous renal biopsy specimens by means of an automated biopsy gun, were evaluated histopathologically under light and direct immunofluorescent(DIF) microscopy by an experienced histopathologist.

**Results :** Total admitted childhood nephrotic syndrome during this period was 1512 and renal biopsy was done in 354 patient. Among the 354 children, histopathological findings were mesangial proliferative glomerulonephritis [MesPGN]was 92(25.98%),minimal change disease[MCD]was79 (22.32%), IgM nephropathy[IgMN]was69(19.49%), focal segmental glomerulosclerosis[FSGS] was 37(10.45%), membranoproliferative glomerulonephritis [MPGN] was 37(10.45%), IgA nephropathy [IgAN] was 20(5.65%),membranous nephropathy[MN] was 08(2.27%) and others were 12(3.39%).

**Conclusion :** In this study we found that theselected patient for renal biopsy in the last 12 years showed that minimal change disease had been decreasing but the other histological types are increasing gradually such as mesangial proliferative glomerulonephritis, FSGS and IgM nephropathy.

**Key words :** Nephrotic syndrome, renal biopsy, renal disease, minimal change disease.

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### Introduction

Nephrotic syndrome is one of the most common renal diseases in children. Idiopathic nephrotic syndrome(INS) has a reported incidence of 20-40/million in the western world but in Indian subcontinent it is about 90-100/ million population.<sup>1</sup> Childhood nephrotic syndrome are most commonly caused by one of the two idiopathic diseases: minimal change

nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Other causes of isolated nephrotic syndrome can be subdivided into two major categories: rare genetic disorders and secondary diseases associated with drugs, infections or neoplasia.<sup>2</sup>

International study of kidney disease in children (ISKDC) has declared a uniform protocol for the treatment of first attack

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nephrotic syndrome and relapses. Oral prednisolone 2mgm/kg in single or divided dose for initial six weeks and then 1.5 mg/kg on alternate day single morning dose for the next six weeks.<sup>3</sup> But nephrotic syndrome like steroid dependent (relapses while on steroid therapy or within two weeks of discontinuation), steroid resistant (failure of resolution of proteinuria despite four weeks of prednisolone therapy) and secondary ones are challenging for paediatric nephrologist. All these cases need renal biopsy for histopathological diagnosis to make appropriate plan for further management. Along with steroid, second line drugs like cyclophosphamide, levamisole, calcineurin inhibitors (cyclosporine, tacrolimus) are also used for those cases. Recently, monoclonal antibody (rituximab) trial in many center may be a promise to better future for nephrotic child.<sup>4</sup>

In this prospective study our aim was to find out the pattern of renal histopathology of selected cases of Idiopathic nephritic syndrome.

### Materials and Method

It was a descriptive observational study conducted from January 2004 to December 2015 in the department of paediatric nephrology, National Institute of Kidney Diseases and Urology. A total of 354 renal biopsy were done during this period of last 12 years.

Indications for renal biopsy Included nephrotic syndrome with -

- (i) Age < 2 years or > 8 yrs years
- (ii) unusual presentation such as significant elevation of serum creatinine (above the upper limit of range according to age)
- (iii) gross haematuria (visible discoloration of urine due to presence of red blood cells)
- (iv) prior calcineurin inhibitors (cyclosporine, tacrolimus) therapy in steroid resistance
- (v) frequent relapses
- (vi) steroid dependent

All patients selected for biopsy were included in our study. Therefore histopathologic findings of the renal biopsy of these selected cases were found out in this prospective study.

Child having nephrotic syndrome with small/single kidney or chronic kidney diseases were excluded from the study.

After admission in the paediatric nephrology unit, physical examination were performed and relevant investigations were done. Supportive treatment were given before renal biopsy. Parents or legal guardians were counseled regarding the need for renal biopsy, and written consent were taken before obtaining ultrasound-guided percutaneous renal biopsy specimens by means of an automated biopsy gun.

The biopsy specimens were evaluated histopathologically by light and direct immunofluorescent (DIF) microscopy. Histopathologic findings were interpreted by the same pathologist in accordance with international criteria. Adequacy of biopsy was defined as the presence of at least 5 glomeruli in the specimen on light microscopy.

**Minimal change disease (MCD)** was characterized by the absence of any conspicuous abnormality on light microscopy.

**Mesangioproliferative glomerulonephritis (MesPGN)** was labeled in the presence of diffuse mesangial hypercellularity lacking immune deposits (Fig: 1 A).

**Focal segmental glomerulosclerosis (FSGS)** was characterized by the presence of at least one glomerulus showing a segmental area of sclerosis with or without accompanying tubular atrophy and interstitial fibrosis (Fig: 1 B).

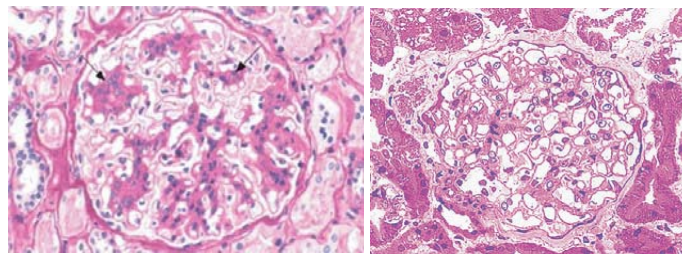
**Membranoproliferative glomerulonephritis (MPGN)** was labeled in the presence of intense cellular proliferation on light microscopy (Fig: 1 C & Fig: 1 E).

IgM nephropathy (IgMN) was labeled when mild to moderate mesangial deposition of immunoglobulin A on direct immunofluorescence study.

Figure 1 shows varieties of Histopathologic findings of the renal biopsy.

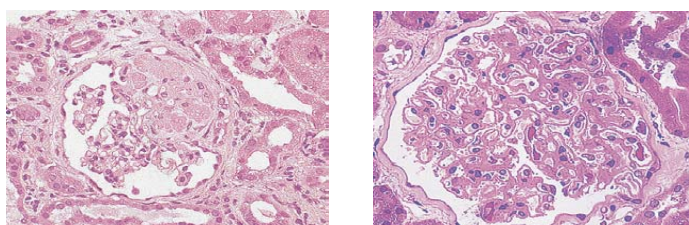
Data including demographic information, clinical diagnosis and laboratory findings were processed and analyzed by SPSS version 2015.

**Fig: 1 Histopathologic findings of the renal biopsy**



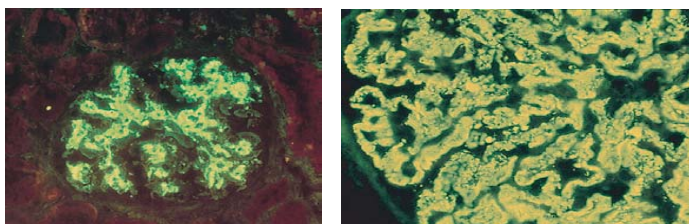
**A. Mesangioproliferative glomerulonephritis (MesPGN)**

**B. Focal segmental glomerulosclerosis (FSGS)**



C. Membranous glomerulonephritis

D. Crescentic glomerulonephritis



E. Membranous glomerulonephritis(DIF)

F. IgA nephropathy(DIF)

### Results and Observation

Total admitted childhood nephrotic syndrome during this period was 1512 among them renal biopsy were performed in 354 cases. All patients selected for biopsy were included in our study. Among the 354 study patient 223 were male and 131 were female and male female ratio was 1.7:1 (table-II). Age range of those children were from 15 months to 12 yrs and mean age was  $7.1 \pm 2.1$ .

Prevalence of mesangioproliferative glomerulonephritis (MesPGN) type was varies in different year. Highest number found in 2014 (14) and 2015 (14). Among all biopsy cases highestpercentage of MesPGNfound in 2007 (50%) and lowest percentage 9.08% found in 2011 (table-III).

Minimal change disease (MCD) also variable. Highest prevalence was 64.29% in 2005 and gradually decreasing the following years 18.52% in 2012, 1.89% in 2013, 6.90% in 2014 and 3.77% in 2015 (table-III).

Focal segmental glomerulosclerosis (FSGS) was more or less same as other histological types. 14.29% in 2004, 22.73% in 2006, 9.53% in 2008, 9.09% in 2010, 7.41% in 2012, 8.62% in 2014 and 5.66% in 2015 (table-III).

Membranoproliferative glomerulonephritis (MPGN) was found 14.29% in 2004, 7.15% in 2007, 13.64% in 2011, 5.66% in 2013, 6.90% in 2014 and 9.43% in 2015(table-III).

The number of IgM nephropathy(IgMN) had been increasing from 17.65% in 2009, 18.18% in 2010, 13.64% in 2011, 18.52% in 2012, 24.53% in 2013,

29.31% in 2014to 49.06% in 2015.

IgA nephropathy (IgAN) was found 14.29% in 2004, 4.55% in 2006, 4.76% in 2008, 5.89% in 2009, 11.32% in 2013,6.90% in 2014 and 5.66% in 2015.

Systemic lupus erythematosus (SLE) was found 3.57% in 2004, 4.76% in 2008, 7.41% in 2012 and 3.45% in 2014. Membranous nephropathy (MN) was found 3.77% in 2013 and 10.33% in 2014. Crescentic GN was found 7.41% in 2012, 1.87% in 2013 and 3.45% in 2014. Acute tubular necrosis(ATN) was found in only one patient in2004 (table-III).

**Table I : Demography of the study children(n=354)**

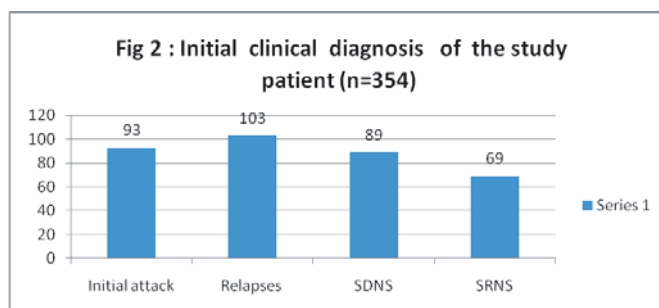
Sex			
Male	223	M:F=1.7:1	
Female	131		
Total	354		

Age	Years	Number	Percentage
	<2	04	1.13
	2-8	129	36.44
	>8-12	221	62.43
	Total	354	100

**Table II : Renal biopsy according to the year**

Year	Nephrotic syndrome	Renal biopsy	Percentage
2004	71	28	39.44
2005	97	28	28.87
2006	125	22	17.60
2007	110	14	12.73
2008	134	21	15.67
2009	84	17	20.24
2010	127	11	08.66
2011	115	22	17.39
2012	160	27	16.87
2013	127	53	41.73
2014	126	58	46.03
2015	236	53	22.46
Total	1512	354	23.41



### Discussion

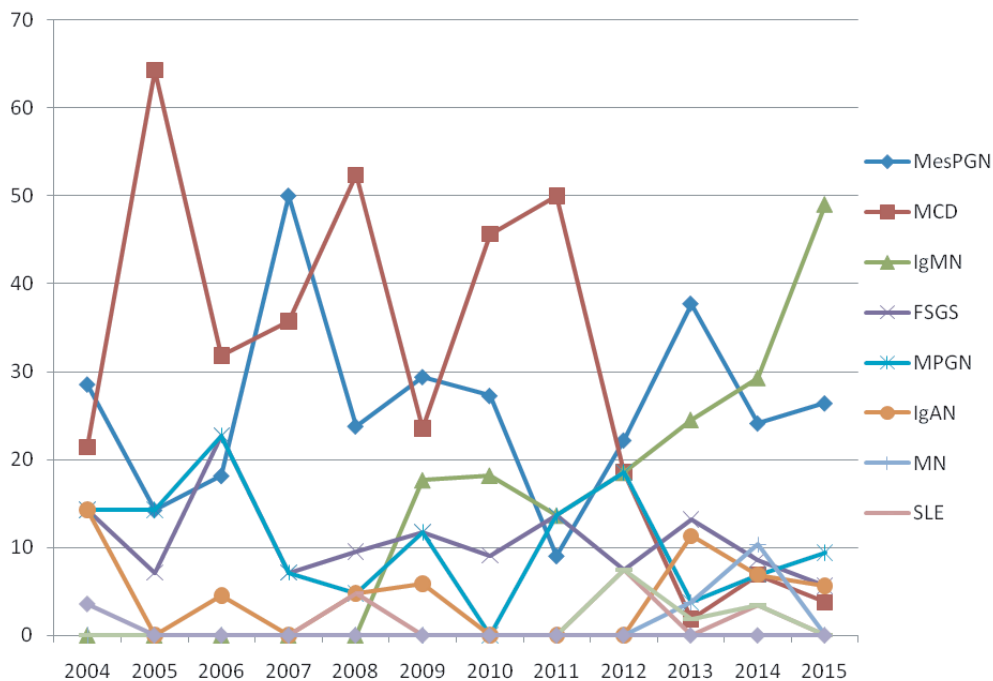
It has been widely accepted that minimal change nephrotic syndrome(MCNS) is by far the most common cause of nephrotic

**Table III : Distribution of renal histopathological types**

year	Total Renal biopsy	Mes PGN		MCD		IgMN		FSGS		MPGN		IgAN		MN		SLE		Crescentic GN		ATN	
		no	%	no	%	no	%	no	%	no	%	no	%	no	%	no	%	no	%	no	%
2004	28	08	28.57	06	21.43			04	14.29	04	14.29	04	14.29			01	3.57			01	3.56
2005	28	04	14.29	18	64.29			02	7.14	04	14.28										
2006	22	04	18.18	07	31.82					05	22.73	05	22.73	01	4.54						
2007	14	07	50.00	05	35.71					01	7.14	01	7.15								
2008	21	05	23.81	11	52.38			02	9.53	01	4.76	01	4.76			01	4.76				
2009	17	05	29.41	04	23.53	03	17.65	02	11.76	02	11.76	01	5.89								
2010	11	03	27.27	05	45.46	02	18.18	01	9.09												
2011	22	02	9.08	11	50.00	03	13.64	03	13.64	03	13.64										
2012	27	06	22.21	05	18.52	05	18.52	02	7.41	05	18.52					02	7.41	02	7.41		
2013	53	20	37.74	01	1.89	13	24.53	07	13.21	03	5.66	06	11.32	02	3.77			01	1.88		
2014	58	14	24.14	04	6.90	17	29.31	05	8.62	04	6.90	04	6.90	06	10.33	02	3.45	02	3.45		
2015	53	14	26.42	02	3.77	26	49.06	03	5.66	05	9.43	03	5.66								0.28

**Table IV: Histological diagnosis according to age(n=354)**

Age	MesPN	MCD	IgMN	FSGS	MPGN	IgAN	MN	SLE	Crescentic GN	Acute tubular necrosis	Total
<2 years		03					01				04
2-8 Years	30	44	25	06	06	06	02	02	02	01	124
>8-12 Years	62	32	44	31	31	14	05	04	03		226
Total	92	79	69	37	37	20	08	06	05	01	354



**Fig 3 : Changing pattern of renal histopathology**

syndrome in children. The ISKDC reported almost 30 years ago that MCNS was present in 77% of all renal biopsies performed in children with idiopathic nephrotic syndrome(INS).<sup>5,6</sup> <http://www.nature.com/ki/journal/v55/n5/full/4490758a.html> - bib2 Others reported MCNS in up to ninety percent.<sup>7</sup> More recent evidence suggests that the histopathological spectrum of glomerulopathies underlying INS is changing in both adults

and children.<sup>8-10</sup> Studies from Siegel et al (1981) and Trachtman et al(1987) have shown a higher incidence of FSGS in pediatric patients with steroid-sensitive nephrotic syndrome. However, both of these studies focused on high-risk populations that were either steroid dependent or frequent relapsers, in which a higher incidence of FSGS was found.<sup>11,12</sup> Results of this study demonstrated that mesangial proliferative

glomerulonephritis was found in 92 (25.98%) cases which was in the top position followed by second highest incidence of MCNS in 79 cases which is about 22.32%. In the last twelve years series of renal biopsy other minor variety also found like FSGS (10.45%), membranous proliferative glomerulonephritis (10.45%) and IgM nephropathy (19.49%). Our observations represent a true decrease in the incidence of MCNS. Study done by Mubarak et al in 2012 showed that MCD was 23.2%, IgMN 13.6%, mesPGN 10.2% in renal biopsy series which is comparable with our study.<sup>12</sup> In 2014 Obiagwu et al found in their study that the renal histopathological result of twenty children where 45% were focal segmental glomerulosclerosis, 20% MCNS, 15% MPGN, 15% membranous nephropathy and 5% mesPGN.<sup>13</sup>

Another consideration for the rise in the incidence of mesangial proliferative glomerulonephritis is a potential increase in the age of the patients admitted in our center more than 8 to 12 years (67.39%). Our results are similar with other study that the increasing incidence of mesangial proliferative glomerulonephritis was limited to patients older than eight years of age.<sup>14,15</sup>

It is well recognized that the diagnosis of FSGS in children with idiopathic nephrotic syndrome carries a poor prognosis.<sup>16,17</sup> Although initially considered a resistant lesion, recent data suggest that more aggressive therapies can induce a response in more than 50% of patients.<sup>18</sup> This study indicates that a biopsy, either at the onset of nephrotic syndrome in patients at risk (older than eight years) or during the early stage of clinical course if poor response to prednisolone therapy are identified, will be beneficial in the management of these patients by specific diagnosis of the histopathological variety.

IgM nephropathy is a relatively new name in the list of glomerulopathies underlying INS both in children and adults.<sup>19,20</sup> However, its status as a distinct entity or even its existence is under debate till date. More recently, a number of reports have been published mostly from tropical countries.<sup>21,22</sup> In our series of renal biopsy, we found IgMN from 2009 and the number of patients were increasing subsequent years. It was the third most common histological variety (19.49%). Incidence of other histopathological pattern like MPGN, membranous nephropathy are more or less same in different studies.<sup>23</sup>

## Conclusion

Our study revealed that there are important changes in the patterns of renal histopathology of nephrotic syndrome in children. Now a days mesangial proliferative glomerulonephritis and IgM nephropathy is emerging.

## References

1. Bagga A, Srivastava RN. Nephrotic Syndrome. In: RN Srivastava & Arvind Bagga, editors. *Pediatric Nephrology*. 5<sup>th</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P) LTD. 2011; 195-196.

2. Burgstein JM. Nephrotic syndrome. In: Behrman RE, Kliegman RM, Jenson HB, editors. *Nelson Textbook of Pediatrics*. 18<sup>th</sup> ed. Philadelphia: WB Saunders; 2008: 2340-2342.
3. Kidney Disease: Improving Global Outcomes (KIDIGO) Glomerulonephritis Work Group. KIDIGO clinical practice guideline for glomerulonephritis. Chapter 3: steroid-sensitive nephrotic syndrome in children. *Kidney Int. Suppl.* 2012; 2: 163-171.
4. Gulati A, Sinha A, Jordan SC et al. "Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. *Clin J Am Soc Nephrol*. Dec 2010; 5(12): 2207-2212.
5. White RHR, Glasgow EF, Mills RJ: Clinicopathological study of nephrotic syndrome in childhood. *Lancet* 1970; 1: 1353-1359.
6. Churg J, Habib R, White RHR: Pathology of the nephrotic syndrome in children: A report for the International Study of Kidney Disease in Children. *Lancet* 1970; 1: 1299-1302.
7. International Study of Kidney Disease in Children: Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 1978; 13(2): 159-165.
8. Bonilla-Felix M, Parra C, Dajani T, et al. "Changing patterns in the histopathology of idiopathic nephrotic syndrome in children". *Kidney International* 1999; 55(5): 1885-1890.
9. Kumar J, Gulati S, Sharma AP, Sharma RK & Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. *Pediatr Nephrol* 2003; 18: 657-660.
10. Kari JA, "Changing trends of histopathology in childhood nephrotic syndrome in western Saudi Arabia". *Saudi Medical Journal* 2002; 23(3): 317-321.
11. Mubarak M, Kazi JI, Shakeel S, et al. The Spectrum of Histopathological Lesions in Children Presenting with Steroid-Resistant Nephrotic Syndrome at a Single Center in Pakistan. *The Scientific World Journal* 2012, Article ID 681802.
12. Trachtman H, Carroll F, Phadke K, Khawar M, Nicastrì A, Chen CK, Tejani A: Paucity of minimal-change lesion in children with early frequent relapsing steroid-responsive nephrotic syndrome. *Am J Nephrol* 1987; 7: 13-17.
13. Obiagwu PN, Aliyu A, Atanda AT. Nephrotic syndrome among children in Kano: A clinicopathological study. *Niger J Clin Prac* 2014; 17: 370-374.
14. Baqi N, Singh A, Balachandra S, Ahmad H, et al.: The paucity of minimal change disease in adolescents with primary nephrotic syndrome. *Pediatr Nephrol* 1998; 12: 105-107.
15. Webb NJA, Lewis MA, Iqbal J, Smart PJ, Lendon M, Postlewaite RJ: Childhood steroid-sensitive nephrotic syndrome: Does the histology matter? *Am J Kidney Dis* 1996; 27: 484-488.
16. Korbet SM, Schwartz MM, Lewis EJ: Primary focal segmental glomerulosclerosis: Clinical course and response to therapy. *Am J Kidney Dis* 1994; 23: 773-783.
17. Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA: Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: A long-term follow-up. *Clin Nephrol* 1995; 43: 84-88.
18. Rennke HG, Klein PS: Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. *Am J Kidney Dis* 1989; 13: 443-456.
19. Gonzalo A, Mampaso F, Gallego N, Quereda C, Fierro C, Ortuno J: Clinical significance of IgM mesangial deposits in the nephrotic syndrome. *Nephron* 1985; 41: 246-249.
20. Al-Eisa A, Carter JE, Lirenman DS & Magil AB. "Childhood IgM nephropathy: comparison with minimal change disease." *Nephron* 1996; 72(1): 37-43.
21. Singhai AM, Vaniker AV, Goplani KR, et al. "Immunoglobulin M nephropathy in adults and adolescents in India: a single center study of natural history". *Indian Journal of Pathology and Microbiology* 2011; 54(1): 3-6.
22. Mokhtar GA. "IgM nephropathy: clinical picture and pathological findings in 36 patients". *Saudi Journal of kidney diseases and Transplantation* 2011; 22(5): 969-975.
23. Markowitz GS, Schwimmer JA, Stokes MB, et al. C1q nephropathy: a variant of focal segmental glomerulosclerosis. *Kidney Int* 2003; 64: 1232.