

Clinicopathological Spectrum of Glomerular Diseases in Adolescents: A Single-center Experience over 4 Years

Abstract

The spectrum of biopsy-proven glomerular disease was studied from a single center in Northwestern India, among adolescents aged 13–19 years. From January 2009 to December 2012, a total of 177 patients with biopsy-proven glomerular disease were studied. The same pathologist reported all the biopsy specimens after subjecting to light, immunofluorescence, and electron microscopy. The clinical profile and laboratory findings of the patients were correlated with the histopathological spectrum of glomerular diseases. Males formed 71.19% ($n = 126$) and the remaining 28.81% ($n = 51$) were females. Lupus nephritis had a strong female predominance, whereas minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) had a male predominance. Nephrotic syndrome was the indication for biopsy in 65% of the cases. Rapidly progressive renal failure and acute nephritis were the next common indications accounting for 14% and 7%, respectively. FSGS was the most common glomerular disease in adolescents ($n = 45$, 25.4%). The next common were MCD and lupus nephritis each contributing 21.6% and 10.7%, respectively. Primary glomerular diseases accounted for 84.75% ($n = 150$) of the total. The remaining 15.25% ($n = 27$) were attributed to secondary glomerular diseases, of which lupus nephritis was the most common, i.e., in 70.4% patients ($n = 19$). FSGS was the most common histology in adolescent nephrotic participants (37%). MCD was the next common, found in 31% of nephrotic patients. Electron microscopy changed the diagnosis made by light microscopy and immunofluorescence in 5.6% cases only, and it confirmed the diagnosis in another 21.6%. Kidney biopsy in adolescents is a safe procedure. The spectrum of glomerular diseases in adolescents is different from that seen in adults and smaller children.

Keywords: adolescence, *c1q* nephropathy, *C3* glomerulonephritis, electron microscopy, IgM nephropathy, kidney biopsy

Introduction

Glomerular disorders have histologic patterns and etiologies that vary according to the age group that is being analyzed. As age advances, the proportion of primary glomerular disorders decrease and disorders secondary to systemic diseases begin to rise. Deranged structure and function of glomeruli forms the pathophysiologic basis of these disorders.

Adolescents with glomerular disease commonly present as nephrotic syndrome (NS). The adolescent NS can be a continuation of a childhood-onset disease or may have its beginning in adolescence. There are some striking differences between glomerular diseases in adolescent and pediatric age group. The overall incidence of NS is less in adolescents as compared to children, but biopsy studies in adolescent NS have frequently

reported more serious forms of glomerular disease (i.e., membranoproliferative glomerulonephritis [MPGN], membranous glomerulonephritis [MGN], and focal segmental glomerulosclerosis [FSGS]), higher frequency of hematuria, and a greater proportion of steroid-resistant NS.^[1,2] The only biopsy series in adolescents with NS from India showed FSGS to be the most common histologic lesion.^[1] This study by Gulati *et al.* looked at data from adolescents with NS alone. However, the literature on the entire spectrum of glomerular diseases in adolescent age group, especially from India, is scanty; hence, the present study was undertaken.

Materials and Methods

The study was undertaken in the Departments of Nephrology and Histopathology, Postgraduate Institute of Medical Education and Research,

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Access this article online

Website: www.indianj nephrol.org

DOI: 10.4103/ijn.IJN_239_16

Quick Response Code:



How to cite this article: Muthu V, Ramachandran R, Nada R, Kumar V, Rathi M, Kohli HS, *et al.* Clinicopathological spectrum of glomerular diseases in adolescents: A single-center experience over 4 Years. *Indian J Nephrol* 2018;28:15-20.

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Chandigarh, over a period of 4 years, from January 2009 to January 2013 (From January 2009 to January 2011 data was retrospectively collected and from January 2011 till 2013 prospective data collection was undertaken) after approval by the Institute Ethical Committee.

Adolescents (defined as 13–19 years of age) with symptoms suggestive of glomerular disorder were subjected to a detailed history, physical examination. The clinical profile and all relevant hematological, biochemical, urine analyses and radiological investigations of adolescents with renal biopsy showing evidence of glomerular disease based on light microscopy, immunofluorescence, and electron microscopy were included in the study. Patients with incomplete clinical or investigation data, transplant kidney biopsy, and inadequate biopsies (<10 glomeruli on light microscopy) were excluded from the study. Incomplete biopsy reports, which lacked either one or more of the following, light/electron/immunofluorescence microscopy was also excluded from the study.

Patients were classified as having one of the following syndromes: NS, nephritic syndrome, rapidly progressive glomerulonephritis/rapidly progressive renal failure (RPRF), chronic glomerulonephritis (CGN), and asymptomatic urinary abnormalities. Descriptive statistics were used, and results were expressed as percentages, frequencies, mean \pm standard deviation, and median. All statistical analyses were done using SPSS (Statistical Package for Social Sciences) for windows version 16 (SPSS Inc., Chicago, IL, USA). Hypothesis testing was done using Chi-square (or Fisher exact) test, $P < 0.05$ was considered significant.

Results

A total of 177 patients aged 13–19 years met our inclusion criteria and were analyzed. The mean age in our study was 16.2 ± 1.9 years (range, 13–19 years). The study included 126 (71.9%) male and 51 (28.1%) female patients. The most common histologic diagnosis among adolescents was FSGS, seen in 45 patients (25.4%), followed by minimal change disease (MCD) in 38 patients (21.6%), lupus nephritis in 19 cases (10.7%), and immunoglobulin A (IgA) nephropathy in 17 patients (9.6%) [Table 1]. Crescentic glomerulonephritis and MGN accounted for 12 patients each (6.8%). Diffuse proliferative glomerulonephritis (DPGN) and MPGN Type 1 were found in nine patients each (5.1%). Other miscellaneous causes (2.3%) constituted 2 patients of IgM nephropathy, one each of C1q nephropathy and anti-glomerular basement membrane disease.

Although males were more in absolute numbers, significant sexual predilection was observed only in three diseases, namely, lupus nephritis, MCD, and FSGS. In all other glomerular diseases, the differences in number of male and female patients were not statistically significant. A very strong female predisposition was noted in lupus nephritis (male:female ratio, 1:8.5). MCD (male:female, 6.6:1) and FSGS (male:female, 5.4:1), on the other hand, were more common in males than females [Figure 1].

There were three patients with Alport's syndrome and all of them were male. Only one among them had a positive family history along with abnormal vision and hearing. The diagnosis of Alport's syndrome in the other two patients was made on electron microscopy during evaluation for steroid-resistant NS.

Table 1: Spectrum of histologic diagnosis in adolescents and their clinical presentations

Histology	NS	Acute nephritis	RPRF	AUA	CGN	Total (%)
FSGS	43	-	-	2	-	45 (25.4)
MCD	38	-	-	-	-	38 (21.5)
Lupus nephritis	11	2	1	5	-	19 (10.7)
IgA nephropathy	2	3	8	-	4	17 (9.6)
Crescentic glomerulonephritis	2	-	10	-	-	12 (6.8)
MGN	12	-	-	-	-	12 (6.8)
DPGN	1	8	-	-	-	9 (5.1)
MPGN Type 1	5	-	3	-	1	9 (5.1)
Dense deposit disease	3	1	1	-	-	5 (2.8)
Alport's syndrome	2	-	-	1	-	3 (1.7)
C3 glomerulonephritis	1	-	1	-	-	2 (1.1)
Amyloidosis	2	-	-	-	-	2 (1.1)
Miscellaneous ^a	3	-	1	-	-	4 (2.3)
Total						177 (100)

^aMiscellaneous - two cases of IgM nephropathy and one each of C1q nephropathy, anti-glomerular basement membrane disease.

AUA: Asymptomatic urinary abnormality, CGN: Chronic glomerulonephritis, DPGN: Diffuse proliferative glomerulonephritis, IgA: Immunoglobulin A, IgM: Immunoglobulin M, FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease, MGN: Membranous glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, NS: Nephrotic syndrome, RPRF: Rapidly progressive renal failure

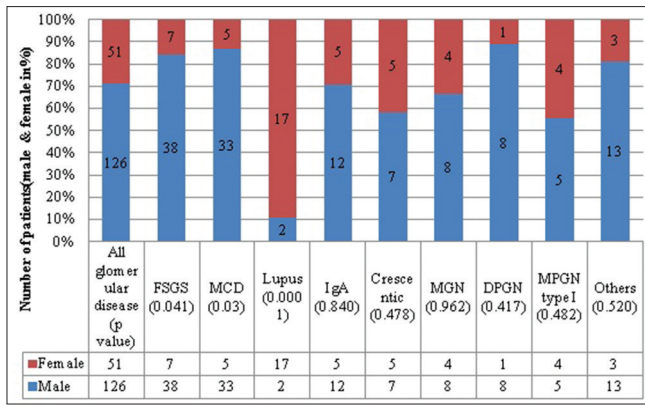


Figure 1: The proportion of male and female patients in each histological category. Absolute numbers of male and female in each category are given in the accompanying table. P values are also shown. DPGN: Diffuse proliferative glomerulonephritis, FSGS: Focal segmental glomerulosclerosis, IgA: Immunoglobulin A nephropathy, MCD: Minimal change disease, MGN: Membranous glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis

Clinical presentation

The most common clinical presentation was NS, which was seen in 125 patients (71%), followed by RPRF in 25 (14%), acute nephritic syndrome in 14 (8%), asymptomatic urinary abnormality in 8 (4%), and CGN in 5 (3%) cases.

Among NS patients with renal insufficiency, MCD was present in 4 patients (19%) as opposed to FSGS in 12 patients (47%). However, none of the histologic pattern showed a significant association with renal insufficiency. More importantly, three out of four patients of MCD with renal insufficiency had either acute tubular necrosis (66%) or acute interstitial nephritis (34%) that explained the renal insufficiency.

Primary and secondary glomerular diseases

Primary and secondary glomerular diseases were found in 150 (84.75%) and 27 patients (15.25%), respectively [Table 2]. Three patients diagnosed with FSGS had family history of NS and/or end-stage renal disease (ESRD). Lupus nephritis was the most common secondary glomerular disease seen in 19 patients (70.4%). The most common histologic pattern observed was Class IV seen in nine patients (47.3%) followed by Class V in four cases (21.1%). Renal insufficiency was noted in 4 (21.1%) patients with lupus nephritis. Renal insufficiency in lupus nephritis was associated with male gender, presence of hypertension, and Class IV lupus nephritis on histology, though these differences were not statistically significant. A summary of distribution of various histologic patterns according to the clinical presentation is provided in Table 1.

Eight patients underwent renal biopsy for asymptomatic urinary abnormalities. Among the eight, 5 (62.5%) were patients diagnosed with systemic lupus erythematosus (SLE) (based on autoantibody profile and systemic features) who were being evaluated for active

Table 2: Glomerular diseases: primary and secondary

Histologic category of glomerular disease	Number of patients (%)
Primary glomerular diseases	
FSGS	45 (30)
MCD	38 (25.3)
IgA nephropathy	17 (11.4)
Crescentic glomerulonephritis	12 (8)
MGN	12 (8)
DPGN	9 (6)
MPGN Type 1	6 (4)
Dense deposit disease	5 (3.3)
C3 glomerulonephritis	2 (1.3)
Miscellaneous ^a	4 (2.7)
Subtotal	150 (100)
Secondary glomerular disease	
Lupus nephritis	19 (70.4)
Chronic hepatitis B associated MCGN	2 (7.4)
Amyloidosis secondary	2 (7.4)
MCGN - cryoglobulinemia associated	1 (3.7)
Alport's syndrome	3 (11.1)
Subtotal	27 (100)

^aMiscellaneous- two cases of IgM nephropathy and one each of C1q nephropathy, anti-glomerular basement membrane disease. DPGN: Diffuse proliferative glomerulonephritis, FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease, MGN: Membranous glomerulonephritis, MPGN: Mesangioproliferative glomerulonephritis, MCGN: Mesangiocapillary glomerulonephritis, IgA: Immunoglobulin A

urinary sediments. These patients had systemic features suggestive of SLE, but lacked symptoms such as edema or hematuria. FSGS was diagnosed in a patient with asymptomatic urinary abnormality and family history of renal transplantation in two of his first-degree relatives for end-stage kidney disease (12.5%). Perihilar FSGS in a young hypertensive with proteinuria and Alport's syndrome in a male with reduced hearing were the other histologic diagnosis in this group of asymptomatic patients (12.5% each).

A comparison of laboratory parameters among various clinical presentations is enumerated in Table 3. The mean serum creatinine value was the highest in adolescents presenting as RPRF followed by subset of NS cases with renal insufficiency. The serum protein and albumin levels were lowest in patients with NS. Electron microscopy changed the diagnosis obtained by light microscopy in ten patients (5.6%) [Table 4]. It played a role in diagnosing basement membrane diseases and in characterizing immune complexes.

Discussion

Adolescents as a group are different from adults and children. This holds true in glomerular diseases as well. Data about glomerular diseases in adolescents are

Table 3: Comparison of laboratory parameters between various glomerular syndromes. [mean (SD)]

Parameter (unit)	NS + RI (n=23)	NS without RI (n=102)	RPRF (n=25)	Acute nephritis (n=14)	All patients (n=177)
Age in years	16.9 (1.3)	15.98 (2.0)	16.8 (1.86)	15.64 (2.02)	16.24 (1.9)
Hemoglobin (g/dl)	11.6 (2.5)	12.16 (2.07)	12.03 (2.2)	10.4 (1.7)	11.2 (2.45)
TLC (cells/cumm)	9449 (2913)	9397 (2872)	9411 (3962)	9300 (3192)	9290 (3192)
Serum creatinine (mg/dl)	2.8 (1.2)	0.74 (0.25)	7.45 (3.96)	1.59 (1.0)	2.3
24 h urine protein (g)	3.66 (3.7)	3.49 (2.8)	2.12 (2.3)	1.04 (0.6)	3 (2.9)
Serum protein (g/dl)	4.35 (0.84)	4.7 (0.98)	5.71 (1.08)	6.05 (1.19)	5.05 (1.13)
Serum albumin (g/dl)	1.9 (0.76)	2.23 (0.77)	3.06 (0.72)	3.38 (0.89)	2.51 (0.90)
Total cholesterol (mg/dl)	427 (148)	410 (132)	181 (34.7)	240 (60)	371 (160)
TGL (mg/dl)	348 (111)	272 (121)	160 (62)	203 (23)	266 (122)
LDL (mg/dl)	311 (165)	293 (121.4)	105.7 (26)	161 (57)	268 (134)

NS: Nephrotic syndrome, NS+RI: Nephrotic syndrome with renal insufficiency, RPRF: Rapidly progressive renal failure, TGL: Triglyceride, LDL: Low-density lipoprotein, TLC: Total leukocyte count

Table 4: Electron microscopy in the diagnosis of glomerular diseases

Clinical presentation	Diagnosis on LM and IF	Diagnosis after EM
Nephrotic syndrome-steroid resistant	Possible MCD	Alport's syndrome
Nephrotic syndrome with renal insufficiency	FSGS	Alport's syndrome with FSGS
Nephrotic syndrome	MCD	MCD with thin basement membrane disease
Asymptomatic proteinuria	MCD	FSGS (sclerosed glomeruli seen on semi-thin sections in EM)
Nephrotic syndrome	MCD	Early MGN
Steroid-resistant nephrotic syndrome	MCGN	Dense deposit disease
Acute nephritis	MCGN	Dense deposit disease
RPRF	MPGN II	Dense deposit disease
Nephrotic syndrome	MCGN	Dense deposit disease
Nephrotic syndrome	MPGN II	Dense deposit disease

LM: Light microscopy, IF: Immunofluorescence microscopy, EM: Electron microscopy, MCD: Minimal change disease, MPGN: Membranoproliferative glomerulonephritis, MGN: Membranous glomerulonephritis, RPRF: Rapidly progressive renal failure, FSGS: Focal segmental glomerulosclerosis, MCGN: Mesangiocapillary glomerulonephritis

virtually absent, unlike in children and adults. To the best of our knowledge, this is the first study describing the clinicopathologic features of all kinds of glomerular diseases in the adolescent age group.

The most common indication for biopsy in our series was NS. It was the most common indication for biopsy in most other series as well, with the percentage ranging anywhere between 60% and 83% in adults from Morocco and Saudi Arabia, respectively.^[3,4] The next common indication was RPRF, followed by acute nephritis in 14% and 8% patients, respectively. Table 5 provides the comparison of indications

for biopsy in our study to similar studies done in pediatric patients^[5,6] and adults.^[7] NS was the most common indication of kidney biopsy across different age groups. However, RPRF accounted for only 3.4% of the cases in the study from Vellore,^[7] whereas it was the second most common indication for biopsy in our series accounting for 14%. Gulati *et al.* analyzed NS in patients aged 1–18 years and tried to identify differences between patients <12 and >12 years of age. MCD was the most common cause of NS among children <12 years of age (42.9%), and FSGS was the most common cause (46.3%) in those >12 years. In our series which is comparable to the >12-year group of the above study, FSGS was the most common histologic pattern both among nephrotics (37%) as well as in the entire spectrum of glomerular diseases (25.4%). FSGS as a separate clinicopathological entity arose in 1970s, after a report published by International Study of Kidney Diseases in Children^[8] and is now the most common cause of NS in adults as well.

MCD accounted for 21.6% of all glomerular diseases and 31% of NS in our series of adolescent glomerular diseases. Mubarak *et al.* noted MCD in 51% of NS in <12 years and only 28.9% in adolescents, a finding which is similar to ours.^[9] This reduction in MCD and increase in FSGS as age increases have been noted in other studies as well.^[7] A trend towards change in histologic spectrum in adults with NS has also been observed recently.^[10] The pathology of glomerular diseases differs between adolescents and children.^[9,11] In Table 6, we have compared the subset of NS patients in our study with the studies from Karachi^[9] and Lucknow.^[11] FSGS was the most common cause of adolescent NS in all three studies. In contrast to these data from India and Pakistan, Hogg *et al.* noted a different scenario in a study of 65 adolescent nephrotic patients from Dallas in 1993.^[12] MCD was the most common histologic diagnosis, accounting for 53%, whereas FSGS and MGN each were present in 18.5% of the adolescents with NS. It is unclear whether the above difference in prevalence is due to the geographical and racial differences or the changing pattern of diseases over time.^[7,11,12]

Table 5: Indication for renal biopsy in various studies

Indications	Present study (13-19 years age)	Korula <i>et al.</i> ^[7] (adults and children)	Abdullah ^[6] (birth to 17 years)	Paripovic <i>et al.</i> ^[5] (mean age 11.5 years)
Nephrotic syndrome, %	65	65.4	48.3	32.9
Acute nephritis, %	7	15.7	11.1 (nephritic syndromes)	-
RPRF, %	14	3.4	-	-
Asymptomatic urinary abnormalities, %	4	1.7	-	39.2% (asymptomatic hematuria + systemic diseases with urinary abnormalities)

RPRF: Rapidly progressive renal failure

Table 6: Comparison of spectrum of nephrotic syndrome – histology

Parameter	Present study	Mubarak <i>et al.</i> ^[9]		Gulati <i>et al.</i> ^[11]	
	13-19 years NS subset (n=116)	12-18 years subset of NS % (n=173)	<12 years subset % (n=365)	12-18 years subset of NS (n=91)	<12 years subset (n=61)
Age (mean±SD) years	16.2±1.9	15.2±1.5	7.26±3.24	14 (age of onset)	-
Male: female	89:26	113:60	231:134	63:28	-
FSGS	42 (37%)	63 (36.4%)	143 (39.2%)	46.3%	39%
MCD	36 (31%)	50 (28.9%)	187 (51.2%)	16.3%	42.9%
MGN	12 (10%)	32 (18.5%)	11 (3%)	-	-
MPGN	4 (3.5%)	13 (7.5%)	4 (1.1%)	-	-
MCGN	-	9 (5.2%)	17 (4.7%)	-	-
IgA nephropathy	3 (1.9%)	3 (1.7%)	3 (0.8%)	-	-

FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease, MCGN: Mesangiocapillary glomerulonephritis, MGN: Membranous glomerulonephritis, MPGN: Mesangioproliferative glomerulonephritis, NS: Nephrotic syndrome, IgA: Immunoglobulin A

MGN was previously the most common cause of glomerular disease in adults. However, recently FSGS has surpassed MGN.^[13] In adults, secondary causes^[13] including drugs, malignancies, hepatitis B, and hepatitis C virus infection account for up to 25% of the MGN cases. Adolescents with MGN in our series, however, lacked evidence for these secondary causes.

Acute nephritic picture was present in 7% of the adolescents with glomerular disease. National registry of Italy^[14] noted that acute nephritic syndrome was present in 4.4% of their children undergoing biopsy. IgA nephropathy was the most common cause in their series,^[14] whereas DPGN was the most common in our adolescent population. Higher percentage of DPGN in the current series may be explained by increased incidence of infection-associated glomerulonephritis in India.

Primary glomerular disease still forms the major proportion in adults, but the proportion of secondary diseases is more than what is observed in children and adolescents.^[15] Secondary glomerular diseases accounted for 15.25% in our series, of which lupus nephritis was the most common (70.4%). A Korean study of 1818 adults with glomerular diseases had 11.8% with secondary glomerular diseases, and the most common cause of secondary disease was lupus nephritis forming 8.7% of the secondary causes.^[16] A high degree of suspicion is needed to identify and treat this condition, as a significant proportion of

these patients are asymptomatic and may have proteinuria on evaluation. Progression to ESRD is well known in the absence of treatment.^[17] Similar to our series, a recent study of lupus nephritis from Spain also noted that renal failure was more common in lupus patients with male gender, hypertension, proteinuria, histology showing Class III or IV, and advancing age.^[18]

Electron microscopy was employed in all the patients included in the study. It had modified the diagnosis in only 6% and aided the diagnosis of MCD in 21% of cases. Contribution of electron microscopy for diagnosis was reported in a study to be 31%, which is comparable to our data (27%).^[19] Electron microscopy can answer diagnostic dilemmas and pave way for better diagnosis.

Conclusion

Adolescents with glomerular disease present commonly as NS and FSGS is the most common cause. Adolescents form a distinct group, and data are grossly inadequate. It is high time; a national kidney biopsy registry is established. By establishing a common registry, uniform form of reporting would be possible. Apart from maintaining a uniform record, it can give information about geographical differences and changes in trend over time.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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