

Original Research Article

Changing histological spectrum of adult nephrotic syndrome in comparison to previous study: single centre analysis

Nath M. Yousuf¹, Dar M. Ahmad², Wani F. Dawood^{3*}

Department of General Medicine, SKIMS Medical College & Hospital, Srinagar, Srinagar, Jammu and Kashmir, India

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*Correspondence:

Dr. Wani F. Dawood,

E-mail: f.dwani101@gmail.com

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ABSTRACT

Background: Glomerular diseases are an important cause of chronic renal failure in developing countries. The spectrum of diseases causing nephrotic syndrome is changing globally in the last few decades.

Methods: Patients in the age group 18-60 years with nephrotic syndrome were consecutively included in the study. Renal biopsies were performed in all patients and were subjected to light microscopy, immunofluorescence (IF) and electron microscopy (EM).

Results: 189 patients (67% males) were included in the study. The mean age was 43 years. Primary glomerular diseases accounted for 92.5% of cases while lupus nephritis was the most common secondary glomerular disease. Focal segmental glomerulosclerosis (FSGS) accounted for 28.6% of primary glomerular diseases making it the most common cause of nephrotic syndrome. It was followed by membranous glomerulonephritis (MGN) in 13.2%, membranoproliferative glomerulonephritis in 11.2%, diffuse proliferative glomerulonephritis in 10.6% and minimal change disease in 9.5%.

Conclusions: The biopsy diagnosis of FSGS has increased considerably in last few decades and it is now the most common cause of nephrotic syndrome in adults in North India. MGN is the most common lesion in patients over 40 years of age.

Keywords: Chronic kidney disease, Focal segmental glomerulosclerosis, Idiopathic nephrotic syndrome, Membranous nephropathy, Minimal change disease, Renal biopsy

INTRODUCTION

Chronic glomerulonephritis, until recently has been the most common cause of chronic kidney disease (CKD) in developing countries like India.^{1,2} However, with the increase in diabetes mellitus, the majority of CKD patients in India now have diabetic nephropathy as their underlying etiology. According to the recently published report of Indian National CKD registry, diabetic nephropathy accounts for 31.3% of CKD while glomerulonephritis is the second most common cause.³ Glomerular diseases in tropical countries is vastly different in epidemiology, etiology and natural history from those seen in temperate countries; and their prevalence also varies according to

socio-economic conditions, race, age and indications for renal biopsy.¹ Over the last few years, studies have shown a changing pattern of these diseases. Previous studies showed that membranous glomerulonephritis (MGN) was the most common cause of adult nephrotic syndrome in the United States and Europe.⁴ However, more recent studies have shown that the focal segmental glomerulosclerosis (FSGS) is increasing significantly and it has become the most common glomerular disease in African-Americans and Hispanic populations.^{4,5} Some studies from India have shown declining incidence of mesangiocapillary glomerulonephritis (MPGN) along with an increase in FSGS, though there are others which have not confirmed this trend.^{6,7}

METHODS

Study design

This was a single center study conducted at Shre-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Jammu and Kashmir, India, a tertiary care referral center. We first described the spectrum of adult nephrotic syndrome at our center from 1987 to 1997, when we had analyzed 221 cases seen.⁸

The present study was an observational retrospective and prospective study conducted to ascertain the histologic spectrum of nephrotic syndrome in adults at our institute from 2014 to 2016 and to note the change in the spectrum of these diseases by comparing with previous studies all over India including SKIMS, Soura.

Study population

All adults between 18 years and 60 years of age, with nephrotic range proteinuria undergoing renal biopsy from May 2014 to May 2016 were included in this prospective study. Nephrotic range proteinuria was defined as proteinuria $>3.5 \text{ g}/1.73 \text{ m}^2 \text{ body surface area/day}$ or $>50 \text{ mg/kg/day}$.

Blood samples were checked for hemoglobin, platelet count, serum creatinine, blood urea, serum albumin, lipid profile, coagulation profile, antinuclear antibody (ANA), hepatitis B surface antigen and anti-hepatitis C virus for all patients. Additional investigations such as blood sugars, anti-double stranded deoxyribonucleic acid, complement levels and anti-neutrophil cytoplasmic antibody were done as and when indicated.

Procedure for renal biopsy

All patients underwent an ultrasound evaluation of the kidneys followed by renal biopsy after proper well-informed consent. The biopsy was performed under ultrasound guidance and local anesthesia using 14 G Bard Trucut biopsy gun. Patients were observed for 24 hours for procedure related complications. The biopsy material was subjected to histopathology (HP), immunofluorescence (IF) and electron microscopic (EM) examination. All the slides for HP examination were studied after staining with H and E and periodic acid Schiff stains. Jones silver staining and Masson's trichrome staining were done in selected cases. IF examination was done by direct method using fluorescein isothiocyanate conjugated antibodies against immunoglobulin G, A and M as well as for complement C3 and C1q. EM examination was done by epon embedding, 65-70 nm sections, uranyl acetate-lead acetate staining and Ziess 906 visualizing.

Based on the renal biopsy and the clinical findings, patients were classified into primary and secondary glomerular diseases.

Statistical method

The data was entered on Microsoft excel sheet and descriptive statistics was used. The statistical package for social sciences version 20.0, (SPSS, IBM, USA) was used for the analysis.

RESULTS

During this 2-years period, 189 patients fulfilling inclusion criteria were included. Of these 126 (67%) were males with mean age 45 was and 63 (33%) were females with mean age 40.

Clinical features

The most commonly encountered symptoms and signs were edema (pedal edema/facial puffiness), oliguria, generalized aches and pains, hypertension, dyspnea and orthopnea. Anorexia and vomiting, nocturia/polyuria were also commonly seen. Fever, rash and high sugars were less commonly seen (Table 1).

Out of 189 patients the most common symptom of the patients was edema/facial puffiness in 171 patients (90.4%) and next common symptom was oliguria seen in 76 patients (40.2%) (Table 1). All patients have features of nephrotic syndrome and around 14 patients (21.7%) have features of overlap i.e. nephrotic-nephritic.

Table 1: Showing symptoms and signs of nephrotic syndrome patients at presentation (n=190).

Symptoms and signs	Number	Percentage
Nephrotic	189	100
Overlap (nephrotic and nephritic)	41	21.7
Edema (facial puffiness and pedal edema)	171	90.47
Oliguria	76	40.21
Gen. aches and pains	40	21.16
Hypertension	42	22.22
Dyspnea and orthopnea	27	14.28
Anorexia and vomiting	12	6.34
Nocturia/polyuria	10	5.29
Fever	8	4.23
Rash	3	1.58
High sugars	3	1.58

Charts showing symptoms and signs of nephrotic syndrome patients at the time of presentation (n=189)

Laboratory parameters

Hypoalbuminemia and hypoproteinemia were a universal finding with mean Of serum protein of 4.79 g/dl and mean serum albumin of 2.68 g/dl. Hypercholesterolemia was also a common finding with mean serum cholesterol of 168.7 (Table 2).

Table 2: Laboratory parameters of nephrotic syndrome patients (n=189).

Parameters	Range	Mean±SD
Hemoglobin (gm/dl)	4-17	10.79±2.08
Urea (mg/dl)	16-331	62.08±49.09
Creatinine (mg/dl)	0.30-13.77	2.12±1.84
T. protein (gm/dl)	1.10-8.20	4.79±1.27
S. albumin (gm/dl)	0.50-4.60	2.68±0.98
S. cholesterol (mg/dl)	90-750	168.7±96.76
Glucose (mg/dl)	70-400	104.47±40.55
Sodium (mEq/l)	116-154	133.38±7.52
Potassium (mEq/l)	1.60-6.01	4.09±0.76
24 hours urinary protein	3.07-19.06	6.07±7.09

Urine analysis of nephrotic syndrome patients revealed proteinuria in all patients, by the dipstick method. 2+ proteinuria was found in 2 patients (1.05%), 3+ proteinuria in 30 (15.87%) and 4+ proteinuria was found in 157 patients (83.06%) (Table 3).

Urinary active sediments were found in 100 patients (52.9%). Glycosuria was found in 2 (1.05%), microscopic hematuria in 80 (42.32%), casts were found in (15.87%) and pyuria was found in 86 (45.50%) (Table 3).

Table 3: Urine analysis of nephrotic syndrome patients (n=189).

Parameters	Number	Percentage
Proteinuria	189	100
1+	Nil	0
2+	2	1.05
3+	30	15.87
4+	157	82.06
Urinary active sediments	100	52.9
Glycouria	2	1.05
Hematuria	80	42.32
Casts	30	15.87
Pyuria	86	45.50

Spectrum of glomerular lesion

Kidney biopsy was performed on 189 patients admitted with nephrotic range proteinuria at our centre during 2014 to 2016. Focal segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative

glomerulonephritis, diffuse proliferative glomerulonephritis, IgA nephropathy and minimal change disease were most common histopathological diagnosis obtained. Out of 189 patients, focal segmental glomerulosclerosis was found in 54 patients (28.6%), males constituted 37 (68.5%) and females were 17 (31.5%). Membranous glomerulonephritis was found in 13 patients (13.2%). Out of that males constituted the majority of 22 (88%) and females were only 3 (12%). Membranoproliferative glomerulonephritis was found in 22 patients (11.2%), males were 14 (63.6%) and females were 8 (36.4%). Diffuse proliferative glomerulonephritis was found in 20 patients (10.6%). The majority among this type of lesion were males 11 (55%) and females were 9 (45%). IgA nephropathy was diagnosed in 19 patients (10.3%), out of which 13 (68.4%) were males and 6 (31.5%) were females. Minimal change disease was found in 18 patients (9.5%), males constituted a majority of 13 (72.2%) and females were only 5 (27.8%). Mesangioproliferative glomerulonephritis was found in 10 patients (5.3%) in which males were 7 (70%) and females were 3 (30%). Chronic sclerosing glomerulonephritis was found in 4 patients (2.1%) with males 3 (75%) and female was only 1 (25%). Secondary causes in total included 16 patients (8.5%) in which lupus nephritis was common 10 patients (5.3%) out of which there was only 1 male (10%) and females were 9 (90%). Diabetic Nephropathy was seen 4 patients (2.3%) in which males were 3 (75%) and females was 1 (25%). Renal amyloidosis was seen in 2 (1.1%) patients and all were males (Figure 1). In most of histopathological lesions males outnumbered females (Table 4).

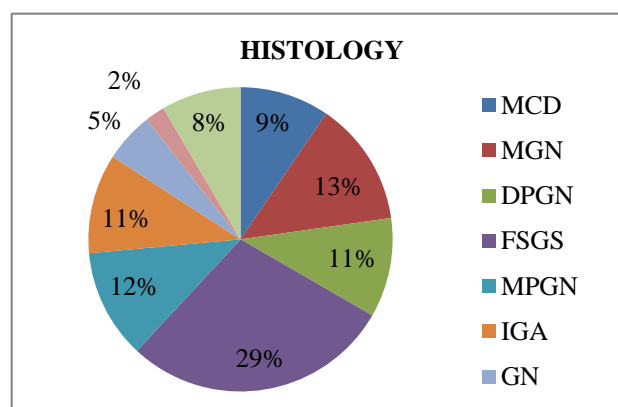


Figure 1: Graph showing histopathological diagnosis on renal biopsy in nephrotic syndrome patients (n=189).

Table 4: Sex distribution of various histopathological diagnosis on renal biopsy of nephrotic syndrome patients (n=189).

Parameters	Male, N (%)	Female, N (%)	Total
Minimal change disease	13 (72.2)	5 (27.8)	18 (100.0)
Membranous GN	22 (88.0)	3 (12.00)	25 (100.00)
Diffuse proliferative GN	11 (55.00)	9 (45.00)	20 (100.00)
Focal segmental glomerulosclerosis	37 (68.50)	17 (31.50)	54 (100.00)
Membranoproliferative GN	14 (63.60)	8 (36.40)	22 (100.00)

Continued.

Parameters	Male, N (%)	Female, N (%)	Total
IgA nephropathy	13 (65.00)	7 (35.00)	20 (100.00)
Mesangioproliferative GN	7 (70.00)	3 (30.00)	10 (100.00)
Diabetic nephropathy	3 (75.00)	1 (25.00)	4 (100.00)
Lupus nephritis	1 (10.00)	9 (90.00)	10 (100.00)
Renal amyloidosis	2 (100.00)	0 (0.00)	2 (100.00)
Chronic sclerosing glomerulopathy	3 (75.00)	1 (25.00)	4 (100.00)

Changing spectrum in comparison with previous study

We have previously analyzed 221 cases of adult nephrotic syndrome between 1987 to 2000.⁸ In this study minimal change disease was most common cause and accounted for around 69 patients (31.1%) followed by membranous glomerulonephritis 48 (21.1%). Focal segmental glomerulosclerosis was next common with 40 patients (18.01%). Mesangioproliferative glomerulonephritis constituted 17 patients (7.69%) and membranoproliferative glomerulonephritis about 16 patients (7.20%). This was followed by diffuse proliferative glomerulonephritis which constituted 7 patients (3.1%) and then focal proliferative glomerulonephritis which accounted for 3 patients (1.35%). In total primary glomerular diseases constituted 200 patients (90.4%). Secondary glomerular disease constituted 21 patients (9.5%) in which diabetic nephropathy was common and included 12 patients (5.42%) followed by lupus nephritis 5 patients (2.36%) then amyloidosis 2 patients (0.90%) and others 2 patients (0.90%).

Table 5: Changing spectrum of glomerular disease at SKIMS, Soura.

Glomerular lesion	1987-2000 N=221	2014-2016 N=189
Primary glomerular disease	200 (90.49)	173 (91.53)
FSGS	48 (21.1)	54 (28.6)
MGN	48 (21.1)	25 (13.2)
MPGN	16 (7.20)	22 (11.6)
DPGN	3 (3.1)	20 (10.6)
Ig AN	-	20 (10.6)
MCD	69 (31.1)	18 (9.5)
Mesangioproliferative GN	17 (7.69)	10 (5.3)
CSG	-	4 (2.1)
Secondary glomerular disease	21 (9.5)	16 (8.4)

FSGS: Focal segmental glomerulosclerosis, MGN: membranous glomerulonephritis, MPGN: membranoproliferative glomerulonephritis, DPGN: diffuse proliferative glomerulonephritis, IgAN: immunoglobulin A nephropathy, MCD: minimal change disease, CSG: chronic sclerosing glomerulonephritis. Figure in parentheses are percentage

In our present study around 189 patients were included. Primary glomerular disease accounted for 173 patients (91.53%) and secondary lesion included 16 patients

(8.4%). Focal segmental glomerulosclerosis was common cause which constituted 54 patients (28.6%). In comparison to previous study focal segmental glomerulosclerosis has shown 1.5-fold increase in frequency (Table 5 and Figure 2). Minimal change disease accounted for 18 cases (9.5%) and has shown 3.5-fold decline in frequency with comparison to previous study. Membranous glomerulonephritis included 25 patient (13.2%) with 1.5-fold decline. Mesangioproliferative glomerulonephritis constituted 10 patients (5.3%) and membranoproliferative glomerulonephritis included 22 patients (11.6%) with frequency remained more or less same as in previous study. Diffuse proliferative glomerulonephritis constituted 20 patients (10.6%) and have shown 3-fold increase in frequency. In secondary lesion lupus nephritis outnumbered with 10 patients (5.3%) and have shown 2-fold increase in frequency with comparison to previous study. Diabetic nephropathy has 2-fold decline with 4 patients (2.3%). The frequency of renal amyloidosis remained same with 2 patients (1.1%).

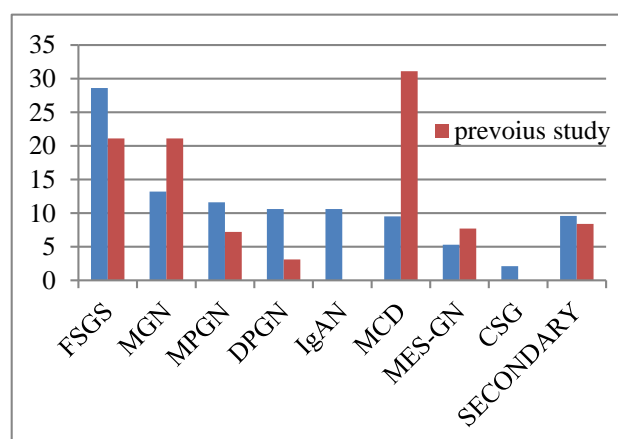


Figure 2: Comparison with previous study at SKIMS, Soura.

DISCUSSION

Glomerular diseases are important cause of end-stage kidney disease. The histological spectrum of glomerular disease is different in adults as compared with children. In our study, primary glomerular diseases accounted for 90% cases of nephrotic syndrome. Overall, FSGS was most common cause of nephrotic syndrome followed by MGN.

An analysis of the spectrum of primary glomerular diseases as a cause of nephrotic syndrome in comparison to previous study has revealed 1.5-fold increase in the

frequency of FSGS. Along with that DPGN has shown 3-fold increase in frequency while MCD and MGN showed decline in frequency. MPGN remained somewhat same. IgA nephropathy accounted for 10.6% cases which was not included in previous study as cause of nephrotic syndrome.⁸ This trend is similar to the emerging global trend, which indicates an increase in the incidence of FSGS making it number one cause of nephrotic syndrome world-wide.⁹⁻¹¹

There can variety of reasons for this changing spectrum. This may be related to improvement in the overall quality of life, decrease rate of infections, increase incidence of obesity, better socio-economic status, and changing pattern of indications for renal biopsy. A more widespread use of Immunofluorescence and electron microscopy in the analysis of renal biopsy can explain increased diagnosis of FSGS and DPGN, which are otherwise likely to be misdiagnosed as MCD.

A summary of other studies on the same subject from India is presented in Table 6. While, the earlier studies found MCD to be most common cause, but more recent studies have shown results similar to our study. Studies from Delhi and Rohtak found MCD to be responsible for more than one-third of nephrotic syndrome.^{12,13} In a recent study published from Kolkata, Golay et al found that FSGS was underlying disease in 27.4% of their patients making it the most common one while MGN was third most common accounting for about 25%.¹⁴ This figure is very similar to

our present data, where FSGS responsible for 28.4% cases. However, they found MCD in 27.1% of cases, making it the second most common cause of nephrotic syndrome while MPGN was seen in only 7%. This is in contrast to our data where MPGN was seen in about 11% of cases while MCD was seen in around 9.5% of cases. The exact reason for this difference is not clear. A possible explanation may be that only 5.6% of patients in their study were subjected to electron microscopy. In a study published by Siegel et al, it is observed that electron microscopy is essential for correct diagnosis in 11% of cases.¹⁵ The incidence of IgAN was 10.6% in our study which was similar to 4-14% in other studies from India.

A comparison with other studies from the Asian region is summarized in Table 7 and it shows certain interesting and conflicting data. While studies from Pakistan and Nepal have shown that IgAN is an infrequent cause of nephrotic syndrome with figures of around 2% the ones from China and Korea have found it to be very common.^{18,19} Chang et al observed that IgAN was responsible for 28.3% of nephrotic syndrome making it the most common cause in Korea.²⁰ Zhou et al found IgAN to be the second most common cause of nephrotic syndrome after MGN, accounting for 20% of cases in China.²¹

However, Kazi et al from Pakistan have found FSGS to be the most common cause accounting for almost 40% of their cases, followed by MGN (26.6%) and MCD (14.8%).¹⁸

Table 6: Comparison of glomerular lesions among nephrotic syndrome in adults in different Indian studies.

Reference	Date et al ⁶	Agarwal et al ¹³	Agarwal et al ¹²	Das et al ¹⁶	Golay et al ¹⁴	Rathi et al ¹⁷	Present study
Year	1971-85	1987-98	2000	1990-2008	2010-12	2002-07	2014-16
Place	Vellore	Delhi	Rohtak	Hyderabad	Kolkata	Chandigarh	Kashmir
N	1532	2250	404	1615	410	364	189
Primary glomerular disease	1276 (83.3)	1316 (58.5)	318 (78.7)	1278 (79.1)	361 (88.1)	324 (89)	173 (91.53)
FSGS	238 (18.6)	263 (20)	56 (17.6)	195 (15.2)	99 (27.4)	99 (30.6)	54 (28.6)
MGN	174 (13.6)	263 (20)	54 (16.9)	129 (10.1)	89 (24.6)	79 (24.4)	25 (13.2)
MPGN	177 (13.9)	153 (11.6)	58 (18.2)	73 (5.7)	24 (6.6)	58 (17.9)	22 (11.6)
MCD	457 (35.8)	487 (37)	106 (33.2)	279 (21.8)	98 (27.1)	48 (14.8)	18 (9.5)
DPGN/PIGN	32 (2.5)	-	-	190 (14.9)	6 (1.6)	9 (2.8)	20 (10.6)
IgAN/MesPGN	57 (4.5)	147 (11.2)	32 (10)	177 (13.8)	29 (8.1)	6 (1.8)	20 (10.6)
CSGN	35 (2.8)	-	-	124 (9.7)	3 (0.8)	12 (3.7)	4 (2.1)
Secondary glomerular	256 (16.7)	934 (41.5)	86 (21.3)	337 (20.9)	49 (11.9)	40 (11)	16 (8.4)

Some of the figures have been recalculated based on the information provided in the publication to maintain uniformity. FSGS: Focal segmental glomerulosclerosis, MGN: membranous glomerulonephritis, MPGN: mesangiocapillary glomerulonephritis, MCD: minimal change disease, IgAN: immunoglobulin A nephropathy, DPGN: diffuse proliferative glomerulonephritis, PIGN: post infectious glomerulonephritis, MesPGN: mesangial proliferative glomerulonephritis, CSGN: chronic sclerosing glomerulonephritis. Figures in parentheses are percentages

Table 7: Comparison of glomerular lesions among nephrotic syndrome in adults in different Asian studies.

Reference	Kazi et al	Garyal and Kafle	Chang et al	Zhou et al	Rathi et al	Present study
Country	Pakistan	Nepal	Korea	China	India	India
N	316	137	1818	1374	364	189
FSGS	39.9	8	5.6	6	30.6	28.6
MGN	26.6	42.3	12.3	29.5	24.4	13.2
MPGN	4.3	21.9	4	1.5	17.9	11.6
MCD	14.8	10.2	15.5	25.3	14.8	9.5
DPGN/PIGN	2.8	2.9	-	0.7	2.8	10.6
IgAN/MesPGN	2.5	2.2	28.3	20	1.8	10.6

FSGS: Focal segmental glomerulosclerosis, MGN: membranous glomerulonephritis, MPGN: mesangiocapillary glomerulonephritis, MOD: minimal change disease, IgAN: immunoglobulin A nephropathy, DPGN: diffuse proliferative glomerulonephritis, PIGN: post infectious glomerulonephritis, MesPGN: mesangial proliferative glomerulonephritis

CONCLUSION

FSGS accounted for 28.6% of primary glomerular diseases making it the most common cause of nephrotic syndrome. It was followed by MGN in 13.2%, membranoproliferative glomerulonephritis in 11.2%, diffuse proliferative glomerulonephritis in 10.6% and minimal change disease in 9.5%. In comparison to previous study at our center, there was a nearly 2-fold increase in the incidence of FSGS, 3-fold increase in diffuse proliferative glomerulonephritis and minimal change disease showing 4-fold decline along with membranoproliferative with 2-fold decline. While there was no major change in incidence of other diseases. The biopsy diagnosis of FSGS has increased considerably in last few decades and it is now the most common cause of nephrotic syndrome in adults in North India. MGN is the most common lesion in patients over 40 years of age. The main limitation of the present study is the small sample size. Furthermore, the fact that our institute caters mainly to the population of North India and to some extent East India, thus these results may not be applicable to other parts of the country. While the IF was performed in 78% of cases, electron microscopy was available in only one-fourth of cases and a greater use of these methods may further change the spectrum of nephrotic syndrome.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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