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Pathological Spectrum of Nephrotic Syndrome: A Single-Centre Study from Western India

Hemant Mahur, Aditya C Upadhyay**, Manish Aswani**, MK Barjatiya***, DP Singh*****

Abstract

***Background:** The aetiology of nephrotic syndrome varies in different parts of the Indian subcontinent. Our study aimed to obtain a comprehensive insight into the aetiology of nephrotic syndrome in our patient population.*

***Method:** We analysed medical records of 222 patients with a diagnosis of nephrotic syndrome between January 2007 and December 2014, at Maharana Bhupal Government Hospital, Udaipur (a tertiary care centre in Western India). Biopsies were evaluated by light microscopy and immunofluorescence microscopy and also special stains, when warranted.*

***Results:** All the patients of nephrotic syndrome biopsied had glomerular disease. Primary glomerular disease was found to be the most prevalent, accounting for 87% of all glomerular diseases. Among primary glomerular diseases, minimal change disease (MCD) was the most common histological lesion (39.19%). Membranous nephropathy (MN) was the second most common histopathological diagnosis, with, 20.72%, followed by focal segmental glomerulosclerosis (FSGS) with 12.16% of all the nephrotic syndrome patients. Among secondary glomerular diseases, amyloidosis (5.13%) was the most common histopathological diagnosis followed by diabetic nephropathy.*

***Conclusion:** Results from our study indicate that MCD is the most common histological finding in patients of nephrotic syndrome followed by MN and FSGS at our center – RNT Medical College, Udaipur.*

***Keywords:** Epidemiology, MCD, nephrotic syndrome, renal biopsy.*

Introduction

Nephrotic syndrome (NS) is a condition of hypoalbuminimea and oedema due to excess loss of proteins in the urine, which is associated with complications such as increased susceptibility to infections, thromboembolism, altered lipid and carbohydrate metabolism and losses of binding proteins of the urine[1].

Glomerular diseases manifesting as nephrotic syndrome differ in epidemiology, aetiology and natural history according to socio-economic conditions, race, gender, age and indications for renal biopsy[2]. There have been studies showing 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[3]. However, more recent studies have shown that focal segmental glomerulosclerosis (FSGS) is increasing significantly and has become the most common glomerular disease in African-Americans and Hispanic populations[3,4]. Some studies from India have shown a declining incidence of membranoproliferative glomerulonephritis (MPGN) along with an increase in FSGS, though there are others which have not confirmed this trend[5,6]. Also different studies from different parts of India have shown different patterns which do not correspond to each other.

RNT Medical College and associated group of hospitals, Udaipur, Rajasthan is a tertiary care referral center in Western India, catering to a large number of patients from Western as well as central India with a different socio-cultural background than rest of India. The present study was conducted to ascertain the histologic spectrum of nephrotic syndrome in patients who have attended our institute from January 2007 to December 2014 and to compare the spectrum with other studies from other parts of India.

Material and methods

All the kidney biopsies performed in patients of nephrotic syndrome at our institute from January 2007 to December 2014 were retrospectively analysed. Nephrotic syndrome describes the onset of heavy proteinuria (> 3.5 g/24 h), hypertension, hypercholesterolaemia, hypoalbuminaemia, oedema/anasarca, and microscopic hematuria.

**Professor, **Post-Graduate Resident, ****Senior Professor, Department of Medicine, ***Senior Professor and Head Department of Nephrology, RNT Medical College, Udaipur, Rajasthan.*
Corresponding Author: Dr Aditya C Upadhyay, Post-Graduate Resident, Department of Medicine, RNT Medical College, Udaipur, Rajasthan . Tel: 7990429108, E-mail: acuaditya@gmail.com.

We recorded the following data for each patient of nephrotic syndrome: name, age, sex, blood pressure, indication for renal biopsy, histopathological diagnosis and laboratory investigations such as lipid profile, serum protein, serum albumin, serum creatinine, 24-hour urinary protein, urine microscopy, virology (HBsAg, anti-HCV, HIV) and serology [anti-dsDNA antibody, antinuclear antibody (ANA), C3, C4]. All renal biopsy specimens obtained were prepared and analysed as per the standard protocol. Analysis included light microscopy (LM) and immunofluorescence (IF). However, electron microscopy (EM) was not performed as this facility was not available in our institute. All biopsies were studied with light microscopy using Haematoxylin and Eosin Stain, PAS stain and PASM stain, along with immunofluorescence microscopy. Special stains such as Masson's Trichrome and Congo red were used when required.

The renal biopsies were reviewed by experienced nephropathologists at our institute and at SRL Ranbaxy Lab at Pune.

Histological categories were classified as follows[7]:-

i Minimal change disease (MCD)

ii Focal segmental glomerulosclerosis (FSGS)

iii Membranous nephropathy (MN)

iv Membranoproliferative glomerulonephritis (MPGN),

v Mesangioproliferative glomerulonephritis (MesGN)

vi Post-infectious glomerulonephritis

vii Lupus nephritis (LN),

viii Amyloidosis,

ix Others – Not specified above

x Biopsy failure

Results

A total of 222 biopsies were performed in our institute from January 2007 to December 2014. Out of the total of 222 biopsies done over the period of 8 years, 9 (4.05%) were biopsy failures (< 10 glomeruli or no renal tissue in biopsy specimen). The rest (213) were successful biopsies.

The study population was spread across various age group as shown in Table I with the largest group being of young adults (20 - 34 years) with 36.48% of the total biopsies from this group ie.81 in total. The mean patient age was 29.8 years.

Of the 222 biopsies, 97 (43.7%) were of female patients and rest of the 125 (56.3%) were of male patients.

The most common histopathological diagnosis among all the patients of nephrotic syndrome was MCD with 87 of the 222 biopsies, i.e., 39.19% which was followed by MN and FSGS with 46 (20.72%) and 27 (12.16%), respectively which is summarised in Table II.

Table I: Distribution of cases – age wise.

Age in years	No. of cases	% of total cases
< 10	6	2.7
10 - 19	60	27.0
20 - 34	81	36.48
35 - 55	62	27.92
> 55	13	5.85
Total	222	100

Table 2: Distribution of final histopathological diagnosis – age wise.

	< 10 years	10 - 19 years	20 - 34 years	35 - 55 years	> 55 years	Total	Per-centage
Final diagnosis							
Primary							
1-MCD	3	29	36	17	2	87	39.19%
2-FSGS	1	13	7	5	1	27	12.16%
3-MN	1	7	17	16	5	46	20.72%
4-MPGN	0	3	2	6	1	12	5.41%
5-MesGN	1	5	7	5	3	21	9.46%
Total primary						193	86.94%
Secondary							
6-LN	0	0	1	0	0	1	0.45%
7-Nephrosclerosis	0	0	0	1	0	1	0.45%
8-Amyloidosis	0	0	7	6	0	13	5.86%
9-PostInfGN	0	0	1	3	0	4	1.80%
10-DN	0	0	0	1	0	1	0.45%
Total secondary						20	9.01%\
Failure	0	3	3	2	1	9	4.05%
Total	6	57	78	60	12	222	100%

MCD: Minimal change disesase, FSGS: Focal segmental glomerulosclerosis, MN: Membranous nephropathy, MPGN: Membranoproliferative glomerulonephritis, MesGN: Mesangioproliferative glomerulonephritis, LN: Lupus nephritis, PostInfGN: Post-infective glomerulonephritis, DN: Diabetic nephropathy.

Results varied greatly with respect to different age groups. In the 6 - 10 year age group there were just six patients of nephrotic syndrome which were clinically non-responsive to treatment and subjected to biopsy. In this group, 50% patients had MCD as their final histopathological diagnosis with 3 of the 6 patients and 16.67% (1 patient) each had MesGN, FSGS and MN as their final histopathological diagnosis.

Among adolescent patients, i.e., 10 - 19 year age group patients, the most common histopathological diagnosis was MCD seen in 50.88% (29) of patients while FSGS in 22.81% (29), MN in 12.8% (7), MesGN in 8.77% (5) and MPGN in 5.26% (3) were the final histopathological diagnoses.

In young adults (20 - 34 years), MCD was again the commonest diagnoses seen in 46.15% (36) of patients followed by MN in 21.79% (17) patients. The next three diagnoses were MesGN in 8.97% (7), FSGS in 8.97% (7) and amyloidosis in 8.97% (7) patients.

MN in 26.67% (16) patients and MCD in 28.33% (17) patients were the two most common histopathological diagnoses among the 35 - 55 years age group. They were followed by amyloidosis in 10% (6), MPGN in 10% (6), FSGS in 8.33% (5) and MesGN in 8.33% (5) patients. 5% (3) patients had post-infectious glomerulonephritis as their final diagnosis.

Of the 13 elderly patients 41.67% (5) patients had membranous nephropathy (MN) followed by MesGN with 25% (3) patients. MCD with 16.67% (2) was the third most common diagnosis in this age group. FSGS and MPGN made up the next 8.3% (1) diagnosis, each.

The entire result is summarised in Table II with a comparative distribution of the histopathological diagnosis across various age groups depicted in Fig. 1.

Table III: Comparison of primary glomerular diseases among various studies.

Study	Date *et al*[5]	Aggarwal[7]	Aggarwal[8]	Das[9] *et al*	Rathi *et al*[10]	Golay *et al*[11]	Present study
Year	1971-85	1987-98	2000	1990-08	2002-07	2010-12	2007-14
Place	Vellore	Delhi	Rohtak	Hyderabad	Chandigarh	Kolkata	Udaipur
No.	1532	2250	404	1615	364	410	222
Primary	83.29	58.49	78.71	79.13	89.01	88.05	86.94
MCD	35.82	37.01	33.33	21.83	14.81	27.15	45.60
MN	13.64	19.98	16.98	10.09	24.38	24.65	23.32
FSGS	18.65	19.98	17.61	15.26	30.56	27.42	13.99
MeSGN	4.47	11.17	10.06	13.85	2.78	8.03	10.88
MPGN	13.87	11.63	18.24	5.71	17.90	6.65	6.22
Secondary	16.71	41.51	21.29	20.87	10.99	11.95	9.01

MCD: Minimal change disesase, FSGS: Focal segmental glomerulosclerosis, MN: Membranous nephropathy, MPGN: Membranoproliferative glomerulonephritis, MesGN: Mesangioproliferative glomerulonephritis.

Discussion

This study is an attempt to identify the histopathological spectrum of nephrotic syndrome across different age groups among our population of southern Rajasthan and to compare it with the various epidemiological data available in other parts of the country and abroad.

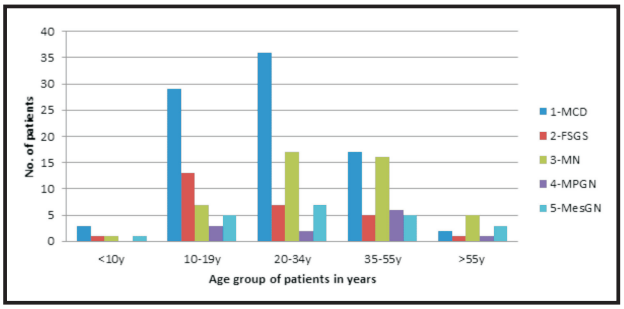

Fig. 1: *Distribution of primary causes of nephrotic syndrome.*

MCD: Minimal change disesase, FSGS: Focal segmental glomerulosclerosis, MN: Membranous nephropathy, MPGN: Membranoproliferative glomerulonephritis, MesGN: Mesangioproliferative glomerulonephritis.

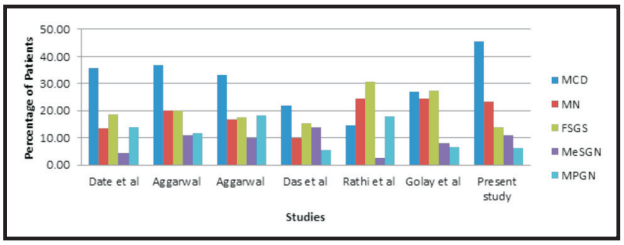

Fig. 2: *Comparison of primary glomerular diseases among various studies.*

MCD: Minimal change disesase, FSGS: Focal segmental glomerulosclerosis, MN: Membranous nephropathy, MPGN: Membranoproliferative glomerulonephritis, MesGN: Mesangioproliferative glomerulonephritis.

We have compared our biopsy results with various other Indian studies' results[5,8-12,15] (as presented in Table III and Fig. 2) and with 2 international studies[14,15] for appreciating intra-country and inter-country variation.

Our study has noted a slight male preponderance in patients of nephrotic syndrome with male: female ratio being 1.29:1 which is comparable with other studies. There was male preponderance in the studies of Agarwal[8] and Das *et al*[10]. Also Rathi *et al*[11] had a ratio of 1.51 in their study and the study by Golay[12] had 57.8% male and 42.19% female patients with M:F = 1.37:1. Also a recent Chinese study by Fenfen Chu *et al*[13] on nephrotic syndrome demonstrated similar prevalence with 379 males and 248 females, with a ratio of M:F = 1.53:1.

As is seen throughout the world, primary glomerular diseases account for more than two thirds of all the cases of nephrotic syndrome. Even in the present study, primary glomerular disease was the predominant cause of nephrotic syndrome and accounted for 86.94% of all biopsies. The proportion of primary glomerular diseases in the study by Date *et al*[5] (83.29%), Aggarwal[9] (78.71%), Das *et al*[10] (79.13%), Rathi *et al*[11] (89.01%) and Golay *et al*[12] (88.05%) had a similar pattern.

Among the primary glomerular diseases causing nephrotic

syndrome, our study found that MCD was the most common and constituted 39.19% of total renal biopsies and 45% of all primary glomerular diseases with nephrotic syndrome presentation. MCD was also the most common cause of nephrotic syndrome when seen across different age groups except the elderly (> 55 years age group) where MN took the lead. Date *et al*[5] in their study of 1532 nephrotic patients too found MCD (35.82%) as the leading cause of nephrotic syndrome and so did Aggarwal[8] (37.01%) (only the nephrotic syndrome cases of this study and their outcome was used for comparison), Aggarwal[9] (33.33%), and Das *et al*[10] (21.83%). Golay *et al*[12] too had MCD (27.17%) as one of the leading cause of nephrotic syndrome by only marginally falling short of FSGS (27.42%). While the study by Fenfen Chu *et al*[13] showed that MN was the most common cause of Primary Nephrotic syndrome in the adult population of Central China, accounting for 26.63% of cases: 167/627, data from Northeastern China[14] reported that their most common cause of primary nephrotic syndrome was MCD (49.1%).

But a completely different pattern was observed in the study by Rathi *et al*[11] who had only 14.81% patients as MCD being the fourth most common cause of Nephrotic syndrome in their study with FSGS (30.56%), MN (24.38%) and MPGN (17.90%) being the top three. This can be explained by the fact that Rathi *et al* applied electron microscopy to one quarter of their biopsy samples. Golay *et al*[12] had also applied electron microscopy in selected cases which may have lead them to identify higher number of FSGS cases (27.42%) making it a close second to MCD (27.17%) in their study. The difference can also be owed to difference in the geography, climate and ethnic groups of these areas as they are from completely different areas of our very diverse country marking an important aspect in variation of the aetiology of nephrotic syndrome. Another study from Telangana by Gandra[15] showed membranous nephropathy (24.4%) followed by minimal change disease (MCD) (17%) and membranous nephropathy (MN) (17%) as the most prevalent histological lesions in patients with nephrotic syndrome.

Our study, when standardised to include only adult age group, had 35.01% cases of MCD which is similar to that of Date *et al*[5](35.82%), Agarwal[8] (37.01%), Aggarwal[9] (33.33%) and Das[10]. This again casts a doubt whether the change in spectrum of histologic lesion of nephrotic syndrome is actual or merely reflecting the difference of work up with one study taking the aid of electron microscopy while other limiting it to light and immunoflourescent microscopy only.

As per an article of Journal of American Society of Nephrology[16] the probability of finding a segmental lesion critically depends on the number of glomeruli evaluated. In addition, the FSGS lesions preferentially affect the juxtamedullary cortex in the early stages of disease. Adequate sampling is thus essential in disclosing the lesion of FSGS and to avoid misdiagnosis as minimal change disease. Ideally, 12 - 15 serial sections each containing a minimum of eight glomeruli should be evaluated. The timing of the biopsy with respect to the disease course is also important. The initial changes (podocyte foot process effacement) are only detectable by EM, because the characteristic sclerotic lesion takes time to develop. It is, therefore, not uncommon that FSGS lesions are absent on the initial biopsy, and a diagnosis of minimal change disease is made, whereas a later biopsy reveals the true nature of the disease by showing clear FSGS lesions.

Hence, further multicentric studies with uniform study protocols is the way to clear this discrepancy and bring forth the actual prevalence of various lesions in nephrotic syndrome.

Conclusion

Nephrotic syndrome was more common among young and middle-aged individuals at our center, affecting males slightly more than females with majority of them being primary glomerular disease. The most common histological lesion among the primary glomerular diseases at our centre was MCD followed by MN, FSGS and MesGN. The secondary glomerular diseases were relatively less common with amyloidosis being the most common.

Limitations of the study: Electron microscopy was unavailable. The use of EM would have provided a detailed histopathological analysis and thereby, may have contributed to a further change in the spectrum of glomerular diseases. Follow-up data was limited which could have provided a confirmatory diagnosis of cases presenting with diagnostic difficulties.

Future perspective: All patients of nephrotic syndrome yielding minimal change disease as their final histological lesion after light and immunofluoroscent microscopy must be further subjected to electron microscopy before the final histopathological diagnosis. Also all patients of minimal change disease who are relapsing must undergo a repeat biopsy again so as to not miss a non- MCD lesion.

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