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A STUDY OF CLINICAL AND HISTOPATHOLOGICAL PROFILE OF NEPHROTIC SYNDROME PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Chronic glomerulonephritis (CGN) is an important etiology of chronic kidney disease. Patients presenting with nephrotic syndrome / nephritic syndrome if not properly treated or even after appropriate treatment, may turn into chronic glomerulonephritis leading to end stage renal disease (ESRD). Nephrotic syndrome is a clinical syndrome with a characteristic pentad of nephrotic range proteinuria, edema, hypercholesterolemia, lipiduria and hypercoagulability. The syndrome is pathognomonic of glomerular disease.

Objectives: This study is being undertaken to find out the Clinical and histopathological profile of Nephrotic Syndrome patients.

Methods: This observational study was carried out in the Department of Nephrology of Command Hospital Airforce Bangalore. Renal biopsy data and clinical profile of patients were collected from the documents of the patients and their old records available. All the clinical, biochemical profile and biopsy data available were studied .

Results: Total 141 nephrotic syndrome patients were included in the study and mean age group was 37.82 ±14.87 year. Predominant age group having glomerular disease was 21-30 yrs. In elderly patients (>60 year of age) glomerular diseases were less commonly observed. The most common glomerular disease was focal segmental glomerulosclerosis which was detected in 34 cases (24.1%).

Conclusions: Predominant cause of nephrotic syndrome in our study was focal segmental glomerulosclerosis (FSGS). Though clinical manifestation of IgA nephropathy is microscopic hematuria and sub-nephrotic proteinuria in the present study, it was the third most common cause of nephrotic syndrome. The secondary infections and venous thrombosis is not so uncommon in the setting of nephrotic syndrome. Majority of the patients (78.01%) have 24 hour urinary protein in the range of 3.5 to 5 gram.

KEYWORDS : Nephrotic syndrome; Renal biopsy; Nephrotic range proteinuria; IgA nephropathy; Hypoalbuminemia; Edema; Anasarca

INTRODUCTION

Nephrotic syndrome is a clinical syndrome with a characteristic pentad of proteinuria: adult > 3.5g/day; child >40mg / hour per m2, hypoalbuminemia <3.5 g/dl, edema, hypercholesterolemia, lipiduria and Hypercoagulability [1]. The syndrome is pathognomonic of glomerular disease. Virtually any glomerular lesion may be associated, at least temporarily, with proteinuria of sufficient magnitude to result in hypoalbuminemia and thus set into motion the pathophysiologic processes responsible for the constellation of findings we call the nephrotic syndrome.Patients may be nephrotic with preserved renal function, but in many circumstances, progressive renal failure will become superimposed when nephrotic syndrome is prolonged. Independent of the risk of progressive renal failure, the nephrotic syndrome has far reaching metabolic effects that can influence the general health of the patient. Fortunately some episodes of nephrotic syndrome are self-limiting and a few respond completely to specific treatment [1].

OBJECTIVES OF THE STUDY

This study is being undertaken to find out the Clinical and histopathological profile of Nephrotic Syndrome patients in this Tertiary Care Hospital.

Source of Data

Patient attending medicine/nephrology OPD or admitted in wards with complaints of anasarca or having incidental finding of significant proteinuria while being worked up for other complaints.

METHODOLOGY

This observational study was carried out in the Nephrology Department of Command Hospital Airforce Bangalore. Renal biopsy data and clinical profile of patients were collected from the documents of the patients, old records from Department of nephrology command hospital Bangalore and Department of Renal pathology Manipal Hospital Bangalore. All the clinical and biopsy data from Jan 2013 to Dec 2017 were studied retrospectively. From Jan 2018 to Mar 2019 all the patients having clinical and biochemical features suggestive of nephrotic syndrome were followed up and their renal biopsy report were collected.

INCLUSION CRITERIA :

All patients with nephrotic syndrome defined as having generalized edema, nephrotic range proteinuria (24 hr urinary protein >3.5gm/24 hr), hypoalbuminemia, hypercholesterolemia and lipiduria. In the retrospective data only those patients who had documentary clinical/biochemical evidence of nephrotic syndrome at the disease onset and were biopsied thereafter.

Exclusion criteria

Those patients having inadequate/ missing clinical/biopsy data,Inadequate biopsy defined as < 8 glomeruli in light microscopy,evidence of diabetic nephropathy as suggested by other target organ damage such as diabetic retinopathy. However diabetic patient having other glomerular diseases on renal biopsy were included

RESULTS

Total 141 nephrotic syndrome patients were included in the study who fulfilled the inclusion criteria and had adequate renal biopsy during the study period. Mean age group was 37.82 ±14.87 year [figure 9]. Predominant age group having glomerular disease was 21-30 yrs. In elderly patients (>60 year of age) glomerular diseases were less commonly observed.

Table-1: Age profile of nephrotic syndrome patients.

Age groups	Frequency	Percent
10 –20	11	7.8
21 –30	43	30.49
31 –40	26	18.43
41 –50	33	23.40
51 –60	17	12.05
61 –70	7	4.96
71 –80	2	1.41
81 – 90	1	0.7
Total	141	100.0

Table-2: Age- biopsy diagnosis profile.

Biopsy diagnosis	10-20 YRS	21-30 YRS	31-40 YRS	41-50 YRS	51-60 YRS	61-70 YRS	71-80 YRS	81-90 YRS	Total
MCD	2	3	1	5	2	1	1	0	15
FSGS	5	7	7	8	5	2	0	0	34
IgA nephropathy	1	17	7	3	0	0	0	0	28
Membranous GN	2	9	5	8	3	2	1	1	31
Lupus nephropathy	2	3	4	2	2	0	0	0	13
MPGN	0	3	1	4	1	1	0	0	10
Amyloidosis	0	0	2	2	0	0	0	0	4
Crescentic GN	0	0	0	1	4	1	0	0	6
Total	12	42	27	33	17	7	2	1	141

Table -3 : Gender-biopsy diagnosis profile of nephrotic syndrome

SEX	MCD	FSGS	IgA nephropathy	Membranous GN	Lupus nephropathy	MPGN	Amyloidosis	Crescentic GN	Total
MALE	10	22	24	24	3	7	1	2	93
FEMALE	5	12	4	7	10	3	3	4	48
	15	34	28	31	13	10	4	6	141

Presenting complaints

Table-4: Presenting complaints profile of nephrotic syndrome.

Presenting symptoms	Frequency	Percent
Asymptomatic	89	63.1
Pneumonia	23	16.3
Urinary tract infection	7	5.0
Acute gastro enteritis	5	3.5
Meningitis	2	1.4
Pulmonary thromboembolism	5	3.5
Deep vein thrombosis	10	7.1
Total	141	100.0

About 78.01 % of cases had 24 hour urinary protein in the range of 3.5-5 gm/24 hrs. Only 4.96% of cases had proteinuria >8 gm/day on initial presentation in our study.

ANA positivity was observed in 07 cases (5%) while ANCA positivity was detected in 04 cases (2.8%). Though the diagnosis of lupus nephritis on biopsy was made in 13 cases absence of ANA positivity/C3 positivity may be due to the fact that many patients were on immune suppressant for extra renal manifestation prior to undergoing kidney biopsy. Immunofluorescence study was done in all the biopsies. It was negative for IgG, IgM, IgA, C3, C1q in 65 cases (56.1%). Predominant IgG positivity and IgA positivity were noticed in 31 cases (22%) and 28 cases (19.9%) respectively

Table 5- Kidney biopsy diagnosis profile of nephrotic syndrome

Biopsy diagnosis	Frequency	Percent
Minimal change disease	15	10.6
Focal segmental glomerulosclerosis	34	24.1
IgA Nephropathy	28	19.9
Membranous nephropathy	31	22.0
Lupus nephritis	13	9.2
MPGN	10	7.1
Amyloidosis	4	2.8
Crescentic glomerulonephritis	6	4.3
Total	141	100.0

In our study the most common glomerular disease was focal segmental glomerulosclerosis which was detected in 34 cases (24.1%). The second most common was membranous nephropathy -31 cases (22%). IgA nephropathy was detected in 28 cases (19.9%). Among the secondary glomerular disease lupus nephritis was the most common which was detected in 13 cases (9.2%).

Table-6 : Comparative table of related previous studies

Variables	Present study	Balkrishnan et al.[27]	Rathi et al.[29]	Golay et al.[30]	Wang et al.[31]	Al Riyamani et al.[32]	Das et al.[28]	Krishna A et al.[33]
Duration	Jan 2018 - Mar 2019	1990 –2001	2002 –2007	2010 -2012	1996 –2010	1999 –2010	1990 –2008	2012 –2015
Number of subjects	141	5016	349	410	917	133	1849	270
Study centre	CHAF, Bangalore	CMC,Vellore	PGI,Chandigarh	IPGMER,Kolkata	Xinxiang,China	Muscat,Oman	NIMS,Hyderabad	IGIMS,Patna
M:F	1.94:1	-	1.5:1	1.37:1	1.19:1	0.56:1	1.5:1	1.87:1
Mean age	37.82±14.87	-	31.5±11	33.68±13.88	33.1±14.1	-	32.27±18.4	31.48±13.46
MCD	10.6%	10.8%	14.8%	23.90%	8.7%	0%	15.1%	5.56%
FSGS	24.1%	16.8%	30.6%	24.63%	1.3%	19.5%	10.5%	31.11%
IgA nephropathy	19.9%	8.4%	1.8%	8.1%	28.2%	3.0%	4.4%	8.52%
Membranous nephropathy	22%	9.5%	24.4%	22.44%	8.2%	9.8%	7.0%	12.60%
Lupus nephritis	9.2%	6.9%	7.16%	6.58%	4.1%	36.1%	14.6%	5.56%
MPGN	7.1%	2.9%	17.9%	8.1%			3.9%	8.52%
Amyloidosis	2.8%	1%	3.43%	-	-	2.3%	1.5%	0.74%
Crescentic GN	4.3%	-	-	-	0.9%	1.5%	4.5%	2.22%

DISCUSSION

Renal biopsy is the gold standard diagnostic tool in patients with clinical features suggestive of nephrotic syndrome. It not only provides an accurate diagnosis, but also provide information about prognosis and may guide the choice of therapeutic agents.

Our study provides information about renal disease diagnosed on the basis of kidney biopsy and clinical features of nephrotic syndrome. This was both retrospective and prospective study as all the clinical and biopsy data from Jan 2013 to Dec 2017 were studied retrospectively, while Jan 2018 to Mar 2019 the clinical and biopsy data were followed up prospectively. Patients fulfilling the criteria of nephrotic syndrome were biopsied and included in the study only when the renal biopsy sample was adequate. Any missing clinical and biopsy data or inadequate biopsy were excluded from the study. Patients having diabetic nephropathy on renal biopsy were not included in this study.

Only few studies were available in the literature which have been done exclusively on nephrotic syndrome patients[3-16]. Most of the available data included patients having nephrotic / sub-nephrotic proteinuria suggestive of glomerular involvement. Total 141 nephrotic syndrome patients who fulfilled the inclusion criteria and having adequate renal biopsy sample were studied. As the nephrology OPD is exclusively for adult patients, only few patients who were referred from the pediatric OPD were in child age group (10 to 18 yr). The mean age group was marginally higher compared to other studies. The mean age group of our patients was 37.82±14.87 year, while the study by Krishna et al.[7] and Das et al.[2] were 31.48± 13.46 and 32.27 ±18.4 year respectively. Predominant age group having glomerular disease was 21-30 year as our clientalle consists of mainly young serving individual and their families. All primary glomerular diseases were more common in this age group (21-30 year) only and FSGS was the most common lesion across the age groups. Even in the age group of less than 21 years FSGS was the most common diagnosis, though only 12 patients (8.51%) were in this age group. In the age group, 40 years or more FSGS and Membranous GN were the most common diagnosis accounting for more than 50% of the cases followed by minimal change disease (15.51%). Out of total 141 cases only 04 cases were in the age group more than 70 year. Only one case having the diagnosis membranous GN was in the age group of more than 80 year.

Table-6 shows the comparison of data from different previous Indian and Asian studies. In our study there was male predominance for renal biopsy in overall subjects. This finding is similar to various Indian and international studies [2,3,4,6,7]. Lupus nephritis, amyloidosis and

crescentic glomerulonephritis were more common in female. IgA nephropathy was predominantly observed in male group as compared to female (24:4).

As the clinical presentation of generalized edema was in the inclusion criteria so it was present in all patients. Patients with nephrotic syndrome are at increased risk of infection due to various factors like reduced serum concentration IgG, impaired ability to make specific antibodies, decreased level of the alternative complement pathway factors B and D. In the present study, on initial presentation pneumonia and urinary tract infection were detected to be in 16.3% and 5% of cases respectively[17-19,21,23]. In similar study predominantly in children with nephrotic syndrome not on steroid therapy done by Alwadhi et al.[13] upper respiratory infection was the most common (28%) followed by urinary tract infection (22.8%), peritonitis (15.8%), pneumonia (14%) and acute invasive diarrhea (10.5%). Several factors contribute to an increased risk of thromboembolic complications like haemoconcentration, immobility, infection or underlying genetic thrombophilic tendency. The reported incidence of thromboembolic complication in nephrotic children is between 2 and 3 percent [14]. Significant independent predictors of thromboembolism included age more than 12-year, severity of proteinuria or history of thromboembolism preceding diagnosis of nephrotic syndrome. In our study 5 cases (3.5%) were detected to have clinical and radiological features suggestive of pulmonary thromboembolism while deep venous thrombosis detected to be in total 10 cases. Only few studies so far has reported meningitis in nephrotic syndrome patients. In a study by Elidrissy AT.[15]. Six nephrotic children with primary peritonitis and two with pneumococcal meningitis were reported. Peritonitis occurred in relapsing long standing cases while meningitis occurred in recently diagnosed cases. Similar to this study our study also reported two cases of meningitis which was diagnosed within few days of initial presentation. No peritonitis cases on initial presentation were detected in our study.

Heavy proteinuria with or without nephrotic syndrome may occur in association with a wide variety of primary and systemic diseases[20,24-26]. In children predominant cause is minimal change disease. In adults approximately 30% have a systemic disease such as diabetes mellitus, SLE, amyloidosis; the remaining cases are usually due to primary renal disorder such as MCD, FSGS, membranous nephropathy[28-34]. In the present study 78% of the patients had 24 hour urinary protein in the range of 3.5- 5 gm. Only 4.96% of total patients have 24 hour urinary protein more than 8 gm per day. Severity of proteinuria is correlated with poor renal outcomes in patients with primary and secondary glomerular disease and treatment to reduce proteinuria are reno protective. The increasing proteinuria also predicts a rapid decline in kidney function.

The conditions that cause severe nephrotic syndrome typically are non-inflammatory glomerulopathies[35-36]. So, typically the urine sediment is bland indicating that it is not nephritic. The typical nephrotic urine sediments contain few red cells, no red cell/ white cell casts, but oval fat buddies and fatty casts are present. In the present study active sediments were presenting 24.8% of the cases, most of these cases were having proliferative glomerulonephritis with nephrotic -nephritic proteinuria.

The nephrotic syndrome is characterized by increased urinary excretion of albumin and other serum proteins accompany by hypoproteinemia and edema formation. The fractional rate of albumin catabolism increased in nephrotic patient possibly as a result of increased albumin catabolism by the kidney, but the absolute albumin catabolism rate decrease in nephrotic patients[37-43]. The rate of albumin synthesis may be increased, but not sufficiently to maintain normal serum concentration or albumin pull [20,44-46]. We have more than 97% of the patients in the serum albumin range between 1.5 to 2.5 gm/dl, only 2.83% patients had severe hypoalbuminemia (<1.5 gm/dl). The use ACE inhibitors may blunt the increase albuminuria caused by dietary protein supplementations and allow albumin stores to be increased[47-49].

In auto immune diseases the deposits of immune complexes in the glomeruli become inflamed and give rise to nephritic-nephrotic range proteinuria. Autoimmune disease can be associated with other primary glomerular diseases. Nephrotic symptoms are typical of membranous lupus nephritis[50-53]. In the present study ANA positivity and low C3 were in 5% and 2.1% of cases respectively only 2 cases (1.4%) had ANA and Anti dsDNA positivity with low C3. The low incidence of ANA/Anti dsDNA positivity as compared to total incidence of lupus nephritis on kidney biopsy (9.2%) may be due to ongoing immuno suppressive treatment in most of the cases of systemic lupus erythematosus.

Immunofluorescence is integral to diagnostic renal pathology. It is an indispensable technique for rendering an accurate diagnosis in renal pathologies[54-56]. Diseases such as IgA nephropathy, C1q nephropathy and C3 glomerulopathy can not be diagnosed without Immuno fluorescence[57-59]. In the present study IgG3+ was present in 22% of total biopsies. IgA nephropathy which was diagnosed based on predominant IgA positivity (IgA3+) was present in 9.2%. All the lupus nephritis (9.2%) patient diagnosed on the basis of light microscopy had full house positivity. We had four cases (2.8%) of amyloidosis however our predominant lambda deposition was present in 2.1% of the cases.

The frequency of the different forms of nephropathy underlying the nephrotic syndrome in adults was evaluated in a Spanish glomerulonephritis registry of 2000 patients biopsied between the years 1994 and 2001 [46]. Among patients between 15 and 65 years of age the most causes of nephrotic syndrome were membranous nephropathy (24%), Minimal change disease (16%), lupus (14%), FSGS (12%), Membranoproliferative glomerulonephritis (7%), amyloidosis (6%) and IgA nephropathy (6%). A similar distribution was observed among the 725 older adult individual who's age more than 65 years except for an increased prevalence of amyloidosis (17%) and decreased prevalence of lupus(1%). In our subjects FSGS was detected in 34 cases (24.1%), the second most common causes of nephrotic syndrome was membranous nephropathy 31 cases (22%). IgA nephropathy was the third common glomerular disease detected in 28 cases (19.9%). The relative frequency of the different disorders as varied over time in some series. A study by Haas M et al. done between 1995 and 1997 revealed that in adults with nephrotic syndrome in absence of obvious underlying diseases found the major causes to be membranous nephropathy and FSGS-in 33% and 35% cases respectively [47]. FSGS accounted for than 50% of cases of nephrotic syndrome in black individual. The frequency of FSGS was much lower (15%) among biopsies for nephrotic syndrome performed at same institution between 1976 and 1979 [47]. In the present study the FSGS was the commonest glomerular disease detected in 24.1% of the cases. The increase in FSGS is not restricted to black populations. A retrospective analysis of the patterns of glomerular disease in predominantly white cohort from Minnesota 13-fold increase in FSGS and no change in membranous nephropathy frequency between 1994 and 2003 compared with interval between 1974 and 1983 [48]. Nephrotic proteinuria was present in 80% of the patients with FSGS.

The nephrotic syndrome can also develop in patient with post infectious and infection associated glomerulonephritis, membranoproliferative glomerulonephritis and IgA nephropathy. However, these individuals typically have a nephritic type of urine analysis with hematuria and cellular casts. In the present study IgA nephropathy and MPGN was detected to be in 19.9% and 7.5% of the cases respectively. Though in the available literature less than 10% of IgA nephropathy cases present with either nephrotic syndrome or an acute, rapidly progressive glomerulonephritis, in our study it was the third most common causes of the nephrotic syndrome in adults (19.9%). Only occasional patients of MPGN may present late in the course at a time when active inflammation has subsided, such patients may have a bland urine sediment with variable degree of proteinuria and elevation of serum creatinine. In our renal biopsy series in nephrotic syndrome patients 7.1 % cases (10 cases) have renal biopsy diagnosis of membrano proliferative glomerulonephritis (MPGN).

The patients of lupus membranous nephropathy will present with features suggestive of nephrotic syndrome. It is present in 10 to 20 % of patients with lupus nephritis. Affected patients typically present with proteinuria often in the nephrotic range. The patients with lupus membranous nephropathy frequently have microscopic hematuria along with extrarenal or serologic manifestations of SLE. In the present study 9.2 % of the patients who presented as nephrotic syndrome had lupus nephritis on renal biopsy.

In patients with AL amyloidosis 50% will present as clinically apparent nephrotic syndrome. In the present study 2.8% cases were biopsy proven renal amyloidosis. In the case of crescentic glomerulonephritis, the marked reduction in glomerular filtration rate

usually limits the rate of protein filtration; nephrotic syndrome is unusual and is most likely to occur in patients with less severe renal insufficiency. In our series of crescentic glomerulonephritis presenting as nephrotic syndrome with renal insufficiency during this period was detected to be 4.3% of cases

CONCLUSION

Predominant cause of nephrotic syndrome in our study was focal segmental glomerulosclerosis (FSGS). The second most common cause was membranous nephropathy followed by IgA nephropathy.Though clinical manifestation of IgA nephropathy is microscopic hematuria and sub-nephrotic proteinuria in the present study it was the third most common cause of nephrotic syndrome.The secondary infections and venous thrombosis is not so uncommon in the setting nephrotic syndrome. Majority of the patients(78.01%) have 24 hour urinary protein in the range of 3.5 to 5 gram, only 5% of the cases have proteinuria more than 8 gm per day.The active sediments is not so uncommon in nephrotic syndrome if the renal biopsy finding is suggestive of proliferative glomerulonephritis. It was detected in 24.8% of the cases.

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