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Nephrotic Syndrome: Clinico-Histopathological Spectrum in Tertiary Care Hospital of Rohelkhand of U.P (Bareilly)

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Abstract
Nephrotic syndrome is a clinical entity characterized by massive proteinuria (primary albuminuria) leading to hypoproteinemia (hypoalbuminemia) leading to edema and fluids in serous cavities of the body. Hyperlipidemia, hypercholesterolemia and lipiduria are usually associated.
The present study was carried out to analyze the clinico-pathological correlation, asses the value of histopathology as well as to note the spectrum of renal disease in patients with significant proteinuria. Eighty four patients having evidences of nephrotic syndrome were included in this study and underwent ultrasound guided percutaneous renal biopsy. Clinical information was correlated with the pathological finding and results were analyzed. Their age ranged from 7 to 78 years (36.5± 16.7 years) with male to female ratio of 1.2:1. The common presentation of nephrotic syndrome was seen in 83 cases (98.8%) edema, with/without general anasarca, anemia (92.8%) , increase in body weight (80.9%) and ascites (73.8%) were common clinical manifestation. Primary glomerular disease (80.9%) were more common than secondary glomerular disease (19.1%). overall, the most common pathological diagnosis was MG/DLN(25%) and FSGS(20.2%) followed by MPGN(13.1%). The disease were more common in 21 to 40 yrs age group (30 cases o 35.7%) followed by 41 to 60 yrs (27 cases or 32.1%).
Our study reinforces the knowledge that renal biopsy helps in accurate diagnosis and thus help in appropriate management of patient. The MG/DLN and FSGS were common cause of nephrotic syndrome in the productive age group.

Keywords: *nephrotic syndrome, focal segmental glomerulo sclerosis, membranous nephropathy, minimal change disease, renal biopsy.*

Introduction

Nephrotic syndrome (NS) is characterized by substantial loss of protein in urine (primary albuminuria) leading to hypoproteinemia (specially hypoalbuminemia) and it result: edema, hyperlipidemia, hypercholesterolemia and increased lipiduria are usually associated. There is no precise, generally accepted definition that defines the extent of proteinuria or hypoalbuminemia required for the syndrome.[1] In

studies of nephrotic syndrome, the nephrotic proteinuria has been variably defined as >3gm/24 hrs or >3.5g/24 hrs. Most studies have relied on edema as a manifestation of NS and have not strictly defined hypoalbuminemia.[2,3] Based on animal models etc, edema is thought to characteristically develop when serum albumin falls below 3gm/dl. However the presence of edema is variable even when the serum albumin is below 3gm/dl.[4,5] Although not commonly thought as a part of syndrome, hypertension, hematuria and azotemia may also occur. NS is usually due to a glomerular disease and is currently categorized into primary and secondary forms. The primary NS (PNS) or idiopathic NS (INS) both terms denote a similar vagueness as to cause is not associated with any underlying disease. Glomerular disease is most common form of renal disease and can have many different clinical presentations. It presents usually as nephrotic syndrome, rapidly progressive renal failure, acute kidney injury, microscopic hematuria, chronic kidney disease and recurrent disease in the post transplant kidney.[6]

The purpose of this study was to determine the distribution of disease in individual with nephrotic proteinuria (3gm/24hrs) according to the level of serum albumin. The disease is correlated with histological findings to provide the patient precise information regarding risk benefits and potential outcome.

Patient and methods:

Forty six males and 38 females (84 patients male: female = 1.2:1) of age varing from 7-78 years mean ± SD = 36.5±16.1 years of age with nephrotic range proteinuria undergoing renal biopsy were included in this prospective study. Nephrotic range proteinuria was defined as proteinuria >3.5 g/173m^2 body surface area/day or >50mg/dl/kg/day. Proteinuria less than this range, but associated with serum albumin <3.0g/dl was also classified as nephrotic range.[2,5-7]

All patients were interrogated for history and physical examination for clinical spectrum. Blood was analyzed for routine hemoglobin, total and differential count, platelet with general blood picture. Serum was examined for creatinine, urea, albumin, lipid profile, coagulation factors, anti – nuclear antibody (ANA), hepatitis B surface antigen and hepatitis C virus. Additional investigation e.g. blood sugar, complement levels anti-neutrophillic cytoplasmic antibody were done as and when indicated. Ultrasounds were done to evaluate kidney followed by renal biopsy which was performed under ultrasound guidance and local anesthesia using 14G Bard Trucut biopsy gun. The biopsied patients were kept under observation for 24 hours for any complication. Biopsied material was subjected to histopathological examination H&E and periodic acid Schiff stain. Jones silver staining and Masson's In Chrome staining were done in selected cases.

The data were entered in Microsoft excel sheet and analyzed statistically. Based on renal biopsy and clinical findings patients were classified as primary and secondary glomerular disease.

Observation and Results:

Eighty four patients of age ranging from 7 to 78 years (36.5 ± 16.1 years) with male: female ratio of 1.2:1 entered the clinical trial (table. 1) Almost all patients (98.8%) had edema with generalized anasarca 92.8% of cases (table 2) Their edema varying from grade 1 to 4. Anemia of mild to moderate degree was seen in 97.8 cases. There were 23 cases (27.4%) hypertensive. Glomerular lesion are more common in below 40 years age(50 cases,59.5%) as compared to above 40 years (34 cases or 40.5%).Altered bowel habits with pain abdomen, diminished or loss of appetite was present in 80.9% of cases. Burning micturition and oliguria was present in38.1% and 62.1% of cases respectively. Evidence of infection was seen in 31 cases in the form of pneumonia (26.2%), peritonitis (7.1%) and cellulitis of limbs (3.5%). Ascites was seen in 73.8% with sign of pleural effusion unilateral in 11.9% and bilateral 7.1% of cases.

Table 1 Glomerular lesions in relation to age and sex (n=84)

Glomerular lesions (GL)	Age (year)				Total	
	<20 years	21-40 years	40-60 years	>60 years	No. of cases	%
1. Primary GL	18	24	21	5	68	80.9
FSGS	4	6	4	3	17	20.2
MG/DLN	3	6	11	1	21	25
MPGN	4	4	2	1	11	13
MCD	1	-	-	-	1	1.2
IgAN	2	3	-	-	5	5.8
DPGN	1	1	2	-	4	4.7
CSCN	3	4	2	-	9	11.1
2. Secondary GL	2	6	6	2	16	19.1
Lupus N	1	4	-	-	5	5.8
Amyloidosis N	1	2	2	-	5	5.8
Myelo N	-	-	1	1	2	2.4
DN	-	-	3	1	4	4.7
Total	20 (23.8%)	30 (35.7%)	27 (32.1%)	7 (8.3%)	84	100
Males	10	13	18	5	46	54.78
Females	10	17	9	2	38	45.38

FSGS – Focal segm/dlental glomerulo sclerosis MG/DLN – Membranous glomerulo nephritis
MPGN – Mesangio-capillary glomerulo nephritis MCD – Minimal change disease
IgAN – IgA nephropathy DPGN – diffuse proliferative glomerulonephritis
CSCN – Crescentric glomerulonephritis LN – Lupus nephropathy
Amyloidosis N –Amyloidosis nephropathy DN – Diabetic nephropathy
MyeloN-Myeloid nephritis

Table 2. clinical manifestations (n=84)

Clinical manifestations	No. of cases	%
Edema with/without anasarca	83	98.8
Anemia	78	92.8
Dyspnea with/without palpitation	48	57.1
Weakness and giddiness	48	57.1
Altered bowel habits and pain abdomen	36	42.6
Increase in body weight	68	80.9
Ascites	62	73.8
Burning micturition	32	38.1
Fever mild to moderate	52	61.9
Loss or diminished appetite	68	80.9
Frank hematuria	8	9.5
Signs of peritonitis	6	7.1
Signs pleural effusion- Unilateral	10	11.9
-Bilateral	6	7.1
Cellulitis of limbs	3	3.5
Pneumonia and URTI	22	26.2
Hypertension	23	27.4
Oliguria	54	62.1

As picted in table-3 The hemoglobin was 8.10 gm/dl in 59.5% and 6-8gm/dl in 23.6% of cases which was normocytic normochromic and normocytic hypochromic respectively. Serum albumin was varying from 1-3.7 gm/dl with 1.7±0.67gm/dl in 72 cases (92.8%). Serum creatinene (table 4) was varying from 0.9 to 12.3mg/dl with 2.1±3.6 mg/dl and it was more than 1.5 mg/dl(9.6±3.92mg/dl) in 33 cases (39.3%). Hyperlipidemia with raised fraction of serum cholesterol, LDL, VLDL and triglycerides in 72 cases. The HDL level was low. Proteinuria of >3gm/day was seen in 97.6% of cases with macroscopic hematuria in 9.5% and microscopic hematuria in 69.9% of cases.

Table 3 Laboratory findings

Laboratory findings	Range	Mean ± SD	No. of cases	%
Hemoglobin	8-10 gm/dl	9.6±2.8gm/dl	50	59.5
	6-8 gm/dl	7.2±2.4gm/dl	20	23.6
General blood picture– normocytic normochromic			50	59.5
- normocytic hypochromic			20	23.6
Serum albumin <3gm/dl	1.8-2.8gm/dl	2.02±1.62gm/dl	72	85.7
Blood urea >40mg/dl	45-110.2mg/dl	86.2±9.45 mg/dl	46	54.8
S.creatinine >1.5mg/dl	1.58-12.5mg/dl	6.58±3.92mg/dl	33	39.3
Hyperlipidemia			72	92.8
-s.cholesterol	362.4-580.4mg/dl	472.5±28.9mg/dl		
-s.triglycerides	258.2-425.6 mg/dl	342.68± 92.48mg/dl		
-s.very low severity lipoprotein	45.8-66.8mg/dl	54.8 ±7.82mg/dl		
-s.low density lipoprotein	46.5-66.8mg/dl	63.6± 12.48mg/dl		
-s.high density lipoproteins	18.9-29.8mg/dl	25.8±3.62mg/dl		
Urinary findings				
-albuminuria >3gm/dl/day			82	97.6
-sediments – RBC and cast			52	61.9
-Pus cells			33	39.2
Urine protein:creatinine ratio	Range2.89-5.2	4.2±1.38	31	36.9

The spectrum of histopathological lesions as observed are depicted as table 1 and 4 in relation to age, sex and serum creatinine levels. Primary Glomerular disease accounted for 80.9 % and rest were secondary glomerular disease. Amongst the primary glomerular disease MG/DLN (25%) and FSGS(20.2%) was most common followed by MPGN (13.1%) and CSCN (11.3%) lupus nepritis in (5.8%) and Amyloidosis nephritis (5.8%) were the common amongst secondary glomerular disease. Serum creatinine level of more than 1.5mg/dl in Diabetic nephropathy (100 %) ,myelometosis nephritis (100%) was common , Lupus Nephritis (52.7%),IgA nephropathy (80%) and they have deranged renal functions. Nephritic proteinuria (urinary protein >3g/day) with hypoalbuminea is a common entity but with normal serum albumin level is a clinical problem As seen in 14.3% of cases in present series who had under gone renal biopsy for proteinurea. this condition may be even more common, given the fact that these patient are frequently asymptomatic and may not undergo renal biopsy because of their benign clinical history.

Table 4 Renal lesions in relations to renal function (s.creatinine level) (n=84)

Glomerular lesions (GL)	Serum creatine level			
	Less than <1.4mg/dl		More than >1.4 mg/dl%	
	No. of cases	%	No. of cases	%
FSGS,n=17	9	52.8%	8	47.2%
MG/DLN,n=21	17	81.9%	4	18.1%
Lupus GN,n=14	6	42.8%	8	57.2%
MCD,n=1	1	100%	-	-
IgA N,n=5	1	20%	4	80%
MPGN,n=5	4	80%	1	20%
Renal amyloidosis,n=5	5	100%	-	-
DPGN,n=4	2	50%	2	50%
CSGN,n=6	6	100%	-	-
DN,n=4	1	25%	3	75%
myeloN,n=2	-	-	2	100%
Total	52	60.7%	32	39.3%

Discussion

Nephritic syndrome is generally recognized as consisting of proteinuria (heavy), hypoalbumin-emia, edema and hypercholesterolemia from the time of its initial description. [11] the author described nephritic syndrome as proteinuria >3.5g per day with a variable tendency towards edema, hypoprotenimia and hyper lipidimiea.

Patients with nephrotic syndrome (NS) lose massive amounts of protein in the urine leading to hypoproteinemia specially hypoalbuminemia and it results, edema, Hyperlipidemia, hypercholeste-rolemia and increased lipiduria are also associated.[5,8] In this study we analyzed 84 cases of age varied from 7 to 78 years (mean36.5±16.7 years) with male :female ratio of 1.2:1. In other studies gender ratio varied from 1.6 to 2.76:1.[1]

In the present study the patients with nephritic syndrome and serum albumin >3.0 gm/dl (12 cases or 14.3%) have a different distribution of disease than individual with nephritic syndrome and a several albumin <3.0 gm/dl (72 cases or 85.7%) with increased rate of FSCS. Individuals with a serum albumin between 3.0 to 3.5 gm/dl formed intermediate group with regard to the proportions of individuals with FSGS. Physiologic studies has suggested[12,13], that edema occur when serum albumin level fall bellow 3.0g% though Smith noted the decrease colloid osmotic activity of the plasma influence the development of edema, other factors may also be important.[14] The present study consisted of 47 subjects (55,8%) who had evidences of infection in other system the commonest being pleural effusion 19.1 % and lobar pneumonia (26.16 %) followed by peritonitis (7.18 %). Other studies reported incidence of infection from 32 to 38%. In our study pleural effusion specially bilateral might be due to hypo proteinemia.

Glomerular disease are important cause of end stage renal disease (ESRD). The histological spectrum of glomerular disease is different in adult as compared to children as well as in tropical as compared with temperate countries[7]. In the present study, primary glomerular disease was accounted for 80.9% (68 cases) of neprotic syndrome patients while lupus and amyloid nephropathy was common amongst secondary glomerulopaties (5.8%) each. In patients of above 40 yrs of age group MG/DLN was the most common cause even though FSGS was the most common cause in nephritic syndrome(table 1).

An analysis of primary glomerular disease as a cause of nephritic syndrome during the last 5 decades has revealed a fivefold increase in frequency of FSGS. Along with that there was a 3 fold increase in frequency of MG/DLN making it the second common cause of nephritic syndrome while DPGN has decreased of its earlier prevelance[7, 15, 16] . This trend is similar to the

emerging global trend which indicate an increase in the incidence of FSGS making it the most common cause of nephritic syndrome[17]. These changes might be because of change in lifestyle, decrease rate of infections, better socioeconomic status, increasing span of life, obesity etc. Our study report is similar to many reports appear in Indian literature which showed the increased incidence of FSGS and MG/DLN decrease DPGN and MCD[7,18,19]

As we have seen the prevalence of glomerular disease in nephritic syndrome the various studies also observed in the same prevalence of glomerular disease in nephritic syndrome in their clinicohistopathological studies. These are in order of occurrence of FSGN, MG/DLN,MPGN, CSCN and MCD[7,15-21]. Asian countries have certain interesting and conflicting data. Pakistan[22] and Nepal[23] STUDIES reported IgAN as an infrequent cause of nephritic syndrome (2%) while China and Korea found it as the frequent cause[24]. Kazi at al[22] has found the most common cause FSGS (40%). Data from West (USA) demonstrated increasing incidence of FSGS as the cause of end stage renal disaese[25,17]. There is emerging evidence that its incidence in children is also increasing and INDIAN studies demonstrated FSGS as the common cause in adolescence as compared to MCD in younger patient[26].

Conclusion

In conclusion our study indicate that MG/DLN and FSGS are the dominant lesions in Nephrotic syndrome patients. There has been considerable heterogeneity in histopathology and clinical spectrum of nephritic syndrome. However recent data from USA as well as INDIA have clearly shown an increased incidence of FSGS and MG/DLN. Patients are more prone to infections which should be dealt accordingly

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