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RESEARCH ARTICLE

HISTOLOGICAL SPECTRUM OF GLOMERULAR DISEASES IN PATIENTS WITH NEPHROTIC AND NEPHRITIC SYNDROME IN IN CAPITAL CITY OF JAMMU, J&K, INDIA

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Abstract

Introduction: The clinical behavior of glomerular disease can vary from nephrotic syndrome (NS) to nephritic syndrome and sometimes can have a nephrotic-nephritic presentation.

Objectives: To study the histological spectrum of NS and nephritic syndrome in the Jammu region.

Patients and Methods: A retrospective observational study was conducted in Jammu, India, including cases of different types of NS and nephritic syndrome. The demographic characteristics of enrolled patients were recorded and statistically analyzed. Immunofluorescence was conducted for all the included cases. World Health Organization classification was used for histopathological typing of glomerular disease.

Results: A total of 100 patients with either NS (62.0%) or nephritic syndrome (11.0%) having a mean age of 36.46 years were included in this study. Proteinuria (96.0%) and edema (88.0%) were the common presentations. Renal biopsy showed that 79.0% of patients had a primary glomerular disease and 20.0% had a secondary glomerular disease. Among the primary glomerular diseases, the majority of patients had membranous glomerulonephritis (35.4%). Lupus nephritis (55.0%) was the most common secondary glomerular disease. The type of glomerulonephritis was significantly associated with age and serum creatinine ($P<0.05$). There was a significant association observed between various forms of glomerulonephritis and microscopic hematuria, edema, hypertension and acute renal failure.

Conclusion: Membranous glomerulopathy was the most common primary glomerular disease and showed a significant rise in incidences with increasing age. Lupus nephritis was the most common secondary glomerular disease observed in this center.

Introduction:-

Nephrotic syndrome (NS) and nephritic syndrome are the two possible modes of presentation of renal disease. Nephrotic syndrome is characterized by proteinuria (>3.5g/day), edema,hypo-albuminemia (<3.5g/dL), hyper-lipidemia and lipiduria (1,2). However, nephritic syndrome is presented as oliguria, hematuria, proteinuria (<3gm/day) and hypertension. Both types of presentations are due to underlying ongoing glomerular disease. Glomerular diseases are classified as primary glomerular diseases involving primarily the kidney, and secondary

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glomerular diseases wherein the kidney function are affected by a variety of systemic conditions including diabetes, primary hypertension, connective tissue disorder, vasculitis, amyloidosis, plasma cell disorders, infections, and drugs (3). Glomerular disease, if not diagnosed and treated early and appropriately, may lead to renal failure. The distinction between the various causes of NS and nephritic syndrome is important, as these glomerular diseases exhibit different clinical behavior and prognosis and require appropriate treatment protocols (2). The clinical behavior of glomerular disease can vary from NS to nephritic syndrome and sometimes can have nephrotic-nephritic presentation. This similar presentation of clinical characteristics among different glomerular diseases may impact accurate and timely diagnosis. Therefore, renal biopsy plays a crucial role in the diagnosis of glomerular disease in the majority of patients and is considered the gold standard. It is very important to understand shifts in the prevalence and epidemiology of the glomerular disease in a geographical area, as their incidence varies according to the geographical area, race, age, and histologic variants (4-6). There is a scarcity of information regarding the etiological and histological pattern of glomerular diseases in the population of Jammu.Therefore, the present study aimed to assessthe histological spectrum of NS and nephritic syndrome in Jammu. The outcomes may be beneficial to practicing nephrologists and other healthcare professionalsin the effective diagnosis and management of glomerular diseases to prevent renal failure.

Methods:-

Study design:-

A retrospective observational study was conducted in the tertiary care center (Super Specialty Hospital, Government Medical College, Jammu). Medical records of patients with NS and nephritic syndrome were reviewed that were diagnosed on histopathology over a period of two years (December 2018 to November 2020). The demographic characteristics of enrolled patients including age, gender, clinical presentation, laboratory investigations, and the histopathological type of glomerular disease were analyzed retrospectively. The biopsy reports of all the patients were reported by the same renal pathologist. Hematoxylin and eosin, periodic acid–Schiff (PAS), silver methamine, and congo red were used for staining histopathological sections. Features such as glomerular pattern, mesangial hypercellularity, focal segmental and global glomerular sclerosis were identified, which indicates the disease progression. The persisting disease was identified through the presence of tubulointerstitial nephritis, interstitial fibrosis, and tubular atrophy. Immunofluorescence was conducted for all the included cases. World Health Organization (WHO) classification was used for histopathological typing of glomerular disease and on that basis, it was categorized into primary and secondary glomerulonephritis. Patients with neoplastic renal diseases were excluded from the study.

Authors have observed all ethical issues including plagiarism, data fabrication, duplicate publication. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical analysis:-

Data were analyzed using the statistical package for the social sciences (SPSS) version 24.0. Continuous variables were expressed as mean ± SD values and qualitative data was expressed as frequency and percentage. Association between qualitative data was assessed with the Pearson chi-square test and continuous variables were assessed using an independent t-Test. $p<0.05$ was considered statistically significant and $p<0.01$ was considered highly significant.

Results:-

A total of 100 patients with either NS or nephritic syndrome attending the department of nephrology outpatient department (OPD) in a super specialty hospital, from December 2018 to November 2020 were selected randomly for the present study.

Among the total enrolled patients, 51% were males and 49% were females and the male to female ratio was observed to be 1.04:1. The mean age in the study population was 36.46 ± 13.43 years, mean systolic blood pressure was 145.27 ± 17.86 mm Hg, diastolic blood pressure was 88.62 ± 7.75 mm Hg, 24 h urine protein was 4.39 ± 2.86 g/day ad serum albumin was 2.66 ± 0.70 g/dL. Among 100 studied biopsies, 62 had the NS, 11 had nephritic syndrome and 27 had a nephrotic nephritic presentation. Proteinuria was observed in 96.0% of patients and nephrotic proteinuria in 62%. Edema was seen in 88.0% of patients; microscopic hematuria was seen in 38.0% of patients and acute renal failure was seen in 26.0% of patients.

On renal biopsy, it was observed that 79.0% of patients had a primary glomerular disease, 20.0% had a secondary glomerular disease and 1.0% had miscellaneous. Among the primary glomerular diseases, the majority of patients had membranous glomerulonephritis (35.4%) followed by focal segmental glomerulosclerosis (FSGS; 25.3%) and minimal change disease (MCD; 20.3%). Lupus nephritis (55.0%) was the most common secondary glomerular disease.

Table 2 displays the distribution of glomerular disease according to age, serum creatinine and clinical parameters. A type of glomerulonephritis was found to be significantly associated with the age of the patients ($P<0.05$). Minimal change disease (21.5%), membranoproliferative glomerulonephritis (MPGN, 3.1%), diffuse mesangial sclerosis (1.5%), lupus nephritis (13.8%), thrombotic microangiopathy with necrotizing vasculitis (6.2%) were significantly higher in <40 years compared to age >40 years of age group. Membranous glomerulopathy (37.1%), diabetes nephropathy (8.6%), IgA nephropathy (11.4%), FSGS (22.9%) and renal amyloidosis (5.7%), were significantly higher in >40 years of age group compared to age <40 years of age.

A significant association was observed between a type of glomerulonephritis and serum creatinine ($P<0.05$). Membranous glomerulopathy (34.5), MCD (24.1%), diffuse mesangial sclerosis (1.7%), have serum creatinine <1.2 mg/dL commonly at presentation. MPGN (4.8%), diabetes nephropathy (7.1%), IgA nephropathy (11.9%), FSGS (21.4%), lupus nephritis (11.9%), thrombotic microangiopathy with necrotizing vasculitis (9.5%) and renal amyloidosis (2.4%) have significantly higher serum creatinine >1.2 mg/dL at presentation.

Among patients with microscopic hematuria, 31.6% had FSGS, followed by 26.3% had lupus nephritis and 15.8% had IgA nephropathy. The majority of patients with edema (31.8%) had membranous glomerulopathy followed by FSGS (21.6 %) and MCD (18.2%). The majority of patients with HTN had FSGS (27.7%) followed by membranous glomerulopathy (26.2%) and lupus nephritis (15.4%). Patients with acute renal failure commonly showed FSGS (26.9%) followed by 15.4% each IgA nephropathy, lupus nephritis and diabetes nephropathy respectively. Similarly, most patients with proteinuria had membranous glomerulopathy (48.4%) and FSGS (29.0%). A significant association was observed between various forms of glomerulonephritis and microscopic hematuria, edema, HTN and acute renal failure. There was no association between various forms of glomerulonephritis and proteinuria ($P>0.05$).

Discussion:-

The histological pattern of glomerular diseases with NS and nephritic syndrome differs geographically, and the lack of a national or international registry for the same warrants the need to study their occurrence and distribution. The key findings from this study in Jammu demonstrated that primary glomerular diseases were more prevalent, of which membranous glomerulopathy was frequently occurring in NS. The incidence of membranous glomerulopathy increased with age. Lupus nephritis was frequently observed in patients with nephritic presentation and FSGS was the most common nephrotic-nephritic presentation. Diseases like FSGS, lupus nephritis, and TMA necrotizing vasculitis presented with high serum creatinine values.

The most common clinical presentation was proteinuria and edema which was in agreement with the study by Chowdry et al (3) The present study showed 96.0% of patients with proteinuria, of them, 62.0% had nephrotic proteinuria. Nephrotic proteinuria was most common in membranous glomerulopathy followed by FSGS and diabetes mellitus. The majority of patients with microscopic hematuria had FSGS followed by lupus nephritis and IgA. These observations are in line with the study from Kashmir by Sirwal et al (7). Likewise, patients with edema had membranous glomerulopathy followed by FSGS and MCD. Hypertension was the common presentation in FSGS, followed by membranous glomerulopathy and lupus nephritis. Acute renal failure presentation was commonest in FSGS followed by IgA nephropathy and lupus nephritis.

Analyzing the results of the present study in patients with nephrotic and nephritic syndrome, it was observed in the population of Jammu that primary glomerular disease accounted for 79.0% of glomerular disease and the secondary glomerular disease accounts for 20.0%, which is in concordance with the study of Chowdry AM et al (3) and Rathi M et al (5). In the present study, the frequency of NS was higher than nephritic syndrome which is in accordance with other Indian and global studies (6,8). The most common nephrotic presentation was membranous glomerulopathy and the most common nephritic presentation was lupus nephritis while the most common nephrotic-nephritic presentation was FSGS. However, other Indian and global studies showed IgA nephropathy as the

commonest primary NS (3,9,10). A retrospective data of 221 renal biopsies from the Kashmir region demonstrated MCD in 31.2% of patients and membranous glomerulonephritis in 21.7% of patients (7).

Indian studies by Chowdry AM et al (3). and Rathi M et al (5). showed that the majority of patients with primary glomerular disease belonged to a similar age group. Correspondingly, the present study also showed similar occurrences of primary and secondary glomerular diseases. However, these studies reported IgA nephropathy and FSGS as the most common primary glomerular diseases while the present study observed membranous glomerulopathy, followed by FSGS and MCD. Among the secondary glomerular diseases, lupus nephritis was prevalent in the present study which was in line with the above-mentioned studies (3,5). Contrasting data is observed in other studies. An Australian study conducted on a series of 3697 patients reported IgA nephropathy as the most common primary glomerular disease followed by FSGS (10). A cross-sectional study from the United States (N=21,374) observed significant changes in occurrences of glomerular disease subtypes over three decades (11).

The present study showed that membranous glomerulopathy was more common than MCD and FSGS in the age group of <40 years (23.1%, 21.5%, 18.5% respectively). This observation was in concordance with the study by Garyal and Kafle in Nepal (12), Chang et al. in Korea (13), Zhou et al (14) in China but not in concordance with Rathi M et al (5) in India. The reason suggested for this could be due to the genetic background and demographic profile of Jammu. Correspondingly, in the age group of more than 40 years, membranous glomerulopathy still remains the most common glomerular disease with an incidence of 37.1 %, followed by FSGS and IgA nephropathy. This observation was in concordance with the Indian study conducted by Rathi M et al (5). A recent prospective cohort study from Northern India reported membranous glomerulopathy was one of the more common forms of primary glomeruli disease followed by MPGN and MCD in the 19-39 years age group. Majority of patients aged ≥40 years presented with membranous glomerulopathy along with MPGN, followed by IgA nephropathy (6). A Chinese retrospective study of 6049 renal biopsied patients by Zhu et al. suggested a two-fold increase in thefrequency of membranous glomerulopathy over 10 years (15). With the cut-off value of creatinine of 1.2 mg/dL, diseases like MPGN, diabetic nephropathy, FSGS, lupus nephritis, ANCA associated vasculitis presented with higher creatinine at the time of first contact with the nephrologist. This could be due to the aggressive nature of certain diseases or late referral to a nephrologist.

Although primary glomerular diseases are the most common, heterogeneity is observed among types of NS and nephrotic syndromes. A changing frequency is observed over a period depending on race, age, sex and geographical location.

Table 1:- Baseline characteristics.

Baseline characteristics	**Number of Patients N=100**
Age, mean (SD)	36.46 (13.43)
Sex	
Male	51 (51.0)
Female	49 (49.0)
Creatinine (mg/dL), mean (SD)	1.84 (1.83)
Blood pressure mm Hg, mean (SD)	
SBP	145.27 (17.86)
DBP	88.62 (7.75)
Protein level in 24 h (gm/day), mean (SD)	4.39 (2.86)
Albumin (gm/dL), mean (SD)	2.66 (0.70)
Clinical Presentation	
Microscopic hematuria	38 (38.0)
Proteinuria	96 (96.0)
Edema	88 (88.0)
ARF	26 (26.0)
Nephrotic proteinuria	62 (62.0)
Incidence of various forms of glomerular disease (n=100)	
Primary glomerulonephritis	79 (79.0)
Membranous glomerulopathy	28 (35.4)

Minimal change disease	16 (20.3)
Membranoproliferative glomerulonephritis	2 (2.5)
Focal segmental glomerulosclerosis	20 (25.3)
IgA nephropathy	10 (12.7)
Diffuse mesangial sclerosis	1 (1.3)
Diffuse proliferative glomerulonephritis	2 (2.5)
Secondary glomerulonephritis	20 (20.0)
Diabetes nephropathy	3 (15.0)
Lupus nephritis	11 (55.0)
Thrombotic microangiopathy with necrotizing vasculitis	4 (20.0)
Renal amyloidosis	2 (10.0)
Renal cortical necrosis	1 (5.0)
Miscellaneous	1 (1.0)
Data presented as n (%) ARF, acute renal failure; BP, blood pressure; IgA, immunoglobulin A.	

Table 2:- Distribution of glomerular disease.

Variables	**Age-wise**			**Serum creatinine**			**Clinical parameters**					
Glomerular disease	**Age < 40 (n=65)**	**Age > 40 (n=35)**	**P-value**	**Creatinine <1.2mg/dL (n=58)**	**Creatinine >1.2mg/dL (n=42)**	**P-value**	**Microhematuria (n=38)**	**Proteinuria (n=96)**	**Edema (n=88)**	**HTN (n=65)**	**ARF (n=26)**	**Nephrotic proteinuria (n=62)**
Membranous glomerulopathy	15 (23.1)	13 (37.1)	chi square = 20.656, P= 0.037	20 (34.5)	8 (19.0)	Chi square = 25.52, P =0.008	1 (2.6)	28 (29.2)	28 (31.8)	17 (26.2)	2 (7.7)	30 (48.4)
Minimal change disease	14 (21.5)	2 (5.7)		14 (24.1)	2 (4.8)		-	16 (16.7)	16 (18.2)	-	-	4 (6.5)
MPGN	2 (3.1)	-		-	2 (4.8)		2 (5.3)	2 (2.1)	2 (2.3)	2 (3.1)	2 (7.7)	1 (1.6)
FSGS	12 (18.5)	8 (22.9)		11 (19.0)	9 (21.4)		12 (31.6)	20 (20.8)	19 (21.6)	18 (27.7)	7 (26.9)	18 (29.0)
IgA nephropathy	6 (9.2)	4 (11.4)		5 (8.6)	5 (11.9)		6 (15.8)	8 (8.3)	5 (5.7)	6 (9.2)	4 (15.4)	-
Diffuse mesangial sclerosis	1 (1.5)	-		1 (1.7)	-		-	1 (1.0)	1 (1.1)	-	-	-
Diffuse proliferative glomerulonephritis	1(1.5)	1 (2.9)		-	2 (4.8)		2 (5.3)	2 (2.1)	2 (2.3)	2 (3.1)	1 (3.8)	-
Diabetes nephropathy	-	3 (8.6)		-	3 (7.1)		-	3 (3.1)	3 (3.4)	3 (4.6)	1 (3.8)	3 (4.8)
Lupus nephritis	9 (13.8)	2 (5.7)		6 (10.3)	5 (11.9)		10 (26.3)	10 (10.4)	8 (9.1)	10 (15.4)	4 (15.4)	-

TMA with necrotizing vasculitis	4 (6.2)	-		-	4 (9.5)		4 (10.5)	3 (3.1)	1 (1.1)	4 (6.2)	4 (15.4)	-
Renal amyloidosis	-	2 (5.7)		1 (1.7)	1 (2.4)		-	2 (2.1)	2 (2.3)	2 (3.1)	-	2 (3.2)
Renal cortical necrosis	1 (1.5)	-		-	1 (2.4)		1 (2.6)					
FSGS, Focal segmental glomerulosclerosis; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.												

Conclusion:-

The present histological spectrum of glomerular disease in Jammu showed that primary glomerular disease was prevalent. Membranous glomerulopathy was the most common primary glomerular disease and NS presentation in Jammu while lupus nephritis was a common type of secondary glomerular disease and nephritic presentation. Incidence of membranous glomerulopathy increased significantly with the increasing age. Diseases such as FSGS, lupus nephritis, and ANCA vasculitis presented with high creatinine values; hence, needs early diagnosis and management.

Competing interests:-
None.

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