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Original Article

Profile of Immunoglobulin A Nephropathy Patients in a Tertiary Care Center

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Abstract

Introduction: Immunoglobulin A nephropathy (IgAN) is being recognized as the most common glomerular disease worldwide. The prevalence and clinical picture varies from region-to-region.

Aim: The aim of the study is to study the clinicopathological profile and risk factors of IgAN patients admitted at our tertiary care.

Materials and Methods: Prospective observational study in 27 patients with biopsy proven IgAN.

Results: Out of 27 patients, renal syndrome included nephrotic syndrome in nine (33.3%), the nephritic syndrome in three (11.1%), rapidly progressive renal failure in four (14.8%), acute kidney injury in two (7.4%), and end-stage kidney disease in two (7.4%). 18 (66.6%) were presented with renal failure at presentation.

Conclusion: Nephrotic syndrome is the most common clinical presentation in IgAN. The majority presented with renal failure at entry into the study. Severe MEST (Mesangial hypercellularity, Endocapillary hypercellularity, Segmental sclerosis, Tubular atrophy/interstitial fibrosis) scoring was significantly associated with renal failure at presentation. Complete or partial remission of proteinuria had less chance for the progression to chronic kidney disease.

Key words: End-stage kidney disease, Immunoglobulin A nephropathy, Renal biopsy

INTRODUCTION

Primary immunoglobulin A nephropathy (IgAN) is defined as the presence of IgA dominant glomerular deposition in the absence of systemic or other non-renal diseases. It is the most common biopsy-proven primary glomerular disease in the world. There is a wide geographical variation existing around the globe, with incidence varying from 2% to 52%. In some countries such as Japan, China, Singapore, Hong Kong, and Australia, the statistics show that nearly half of the biopsy-proven primary glomerular disease is IgAN.[1] In the European countries, IgAN accounts for 10-20% of the total kidney biopsies. In the United States, this disease is common in certain areas. The incidence is dependent, to a large extent, on variations in the policies of renal biopsy among different countries. Similarly, clinical features also vary from mild-to-severe forms.[2-4] The most common presentations include synpharyngitic macroscopic hematuria, microscopic hematuria with proteinuria, and hypertension and chronic renal failure. The relatively rare presentations include malignant hypertension, acute nephritic syndrome, acute renal failure, and nephrotic syndrome. It presents with a constellation of clinical syndrome ranging from asymptomatic urine abnormalities to smoldering rapidly progressive glomerulonephritis (RPGN).[5-7] Incidence in India varies between 8.6 and 16%. With the advance in genetic, more molecular pathways are unraveled, and pathogenesis were defined little better than previous, so this most common glomerulonephritis is revealing its secrets. A better understanding of glycation, galactosylation molecular machineries in depth of enzymes and chaperone, the better search of happenings of talks of mesangium, podocytes, and proximal tubule through cytokines and receptors, better knowledge of mucosa marrow axis and toll-like receptor clearly will open a better prospectus in treatment.[8,9]

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Aim

The aim of the study is to study the clinicopathological profile and risk factors of IgAN patients admitted at our tertiary care.

MATERIALS AND METHODS

This prospective observational study was conducted in Department of Nephrology, Madras Medical College, Chennai. All patients who have biopsy proven IgAN under care of the Department of Nephrology will be included in the study. Patients with liver disease, psoriasis malignancy, human immune deficiency virus, systemic lupus erythromatosus, rheumatoid arthritis, reactive arthritis, and diabetic nephropathy were excluded from the study. Patients were subjected to urinary examination includes urine for protein, deposits such as red blood cell and white blood cell. Urine was analyzed for red blood cell cast, white blood cell cast. Urine protein/creatinine ratio was done. Patients underwent hematological investigation such as blood hemoglobulin, total count, differential count, and peripheral smear study. Blood investigation includes blood urea, serum creatinine, serum electrolyte, and lipid profiles were taken. Liver function test including serum bilirubin were taken. Glomerular filtration rate (GFR) was estimated by Cockcroft gualt equation (ml/min). Urine and blood was sent for culture and sensitivity. Ultra sonogram of the abdomen was done. Renal biopsies were done on those presented with unexplained renal failure, nephrotic syndrome, and nephritic syndrome. Renal biopsy tissues sent for histopathological examination. These were done by light microscopy and immunofluorescence study. Glomeruli, tubule, interstitial, and vessel were examined with hematoxylin and eosin, periodic acid Schiff, and trichrome. MEST scoring was done. Immunofluorescence studies for IgA, IgM, IgG, C3, and C1q were done. Intensity graded from 0 to 4. Those with 2 + and more of dominant or codominant deposit of IgA, diagnosis of IgAN was made. After excluding those who met exclusion criteria diagnosis of primary IgAN were made. Patients were treated according to clinical syndrome. Patients with acute kidney injury (AKI) where there was no renal improvement then the biopsy was attempted at 5th day to exclude crescents or acute tubular necrosis.

RESULTS

A total of 29 patients with biopsy proven IgAN were included in the study. Of which two who present with end stage renal disease at presentation were excluded from the study. 27 were finalized into this study. 17 (62.9%) were male. The follow-up period ranged from 6 to 18 months. The mean age at presentation was 27.3 years. 11 were presented in 10-19 years age groups (40.7%), followed by seven in 20-29 years age groups (20.9%). Two were in 30-39 years age groups (7.4%). Four were in 40-49 age groups (14.8%). Two were in 50-59 age groups (7.4%), and one was in 60 years. Clinical presentation of patients was classified as in Table 2. Macrohematuria was noted in 11 (40.7%). Hypertension prevailed in 16 (59.3%). Edema was present in 20 (74.1%). Oliguria was seen in 18 (66.6%). Two were (7.4%) presented with hypertensive encephalopathy. Seven (25.9%) had hypertensive retinopathy (Table 1).

Depending upon clinical syndrome patients were categorized as in Table 2. Nine had the nephrotic syndrome (33.3%), the nephritic syndrome was noted in three (11.1%). Four were presented with rapidly progressive renal failure (14.8%). Two presented with AKI (7.4%). Those who presented with end-stage renal failure at presentation were excluded from the study.

Renal biopsy findings were tabulated as follows in Table 3. Scoring was based on Oxford MEST. Mesangial score (M0 and M1) was seen in nine (33.3%) and 19 (70.3%) patients respectively. Endocapillary cellularity (E1) was noted in 14 (51.8%). Sclerosis score (S0 and S1) observed in 14 (51.8%)

Table 1: Clinical presentation

Clinical presentation	*n* (%)
Macrohematuria	11 (40.7)
Edema	20 (74.1)
Oliguria	18 (66.6)
Hypertension	16 (59.3)
Hypertensive encephalopathy	2 (7.4)
Hypertensive retinopathy	7 (25.9)

Table 2: Clinical syndrome

Syndrome	*n* (%)
Nephrotic syndrome	9 (33.3)
Nephritic syndrome	3 (11.1)
Rapidly progressive glomerulonephritis	4 (14.8)
AKI	2 (7.4)
CKD	2 (7.4)

CKD: Chronic kidney disease, AKI: Acute kidney injury

Table 3: Biopsy finding

Biopsy findings	*n* (%)
M0	9 (33.3)
M1	19 (70.3)
E0	13 (48.1)
E1	14 (51.8)
S0	14 (51.8)
S1	11 (40.7)
T0	5 (18.5)
T1	10 (37.3)
T2	12 (44.4)
Crescents	4 (14.8)
Vascular thickening	7 (25.9)

and 11 (40.7%) patients, respectively. Tubular atrophy and interstitial fibrosis score of T1 and T2 was noted in 10 (37.3%) and 12 (44.4%), respectively. Crescents were noted in 4 (14.8%). Vessel wall thickening was present in 7 (25.9%).

Renal biopsy tissues were also studied with immunoflourescence staining for IgA, IgM, IgG, C3, and C1q showed IgA + C3 in 13 (48.1%), IgA + C3 + IgM in 10 (37.3%), IgA + C3 + IgM + IgG in 4 (14.8%),%), and IgA + C3 + IgM + C1q in 2 (7.4%) (Table 4).

Among the 27 patients, 18 (66.6%) were presented with renal failure at presentation. Mean age in who presented with renal failure at presentation was 27.9 years. Male dominated as 13 (72%). Hypertension was noted in 11 (61%). Macrohematuria occurred in seven (38%). Nephrotic range of proteinuria was present in eight (44%).

Renal biopsy showed mesangial hypercellularity (M1) in 15 (83%), endothelial proliferation (E1) was seen in 10 (56%), segmental score (S1) noted in 50%,tubular atrophy/interstitial fibrosis score T1 and T2 was noted in eight (44%) and nine (50%), respectively. Crescents were noted in four (22%).Vessel wall thickening was noted in four. Various factors which were studied between those who presented with renal failure at presentation (GFR <60 ml/min) and those without renal failure at presentation were tabulated in Table 5.

Eight (29.6%) were progressed to chronic kidney disease (CKD) (GFR <60 ml/min) on follow-up period. Mean age was 32.6. 64% were male. Macrohematuria was presented in five (63 %). Hypertension persisted in five (63%). Response to proteinuria was assessed by those achieved complete remission (proteinuria <300 mg/day), partial remission (proteinuria 300-3000 mg/day), and nil remission (proteinuria >3000 mg/day). Three patients (37.5%) never attained remission. One attained complete remission. Four (50%) attained partial remission. Mesangial hypercellularity was noted in 6 (75%). Five presented with endothelial hypercellularity (62.5%). Segmental sclerosis was observed in five (62.5%). Four patients (50%) showed tubular atrophy and interstitial fibrosis. Crescents were noted in two (25%). 7 (87.5%) had GFR <60 ml/min/1.73 m^2 since presentation.

19 (70.4%) had normal renal function at the end of follow-up period. Mean age was 28. Macrohematuria was present in nine (47.3%). Eight had hypertension (42%). Nine patients had complete remission (47%) another seven attained partial remission (36.8%).Three never attained remission. Crescents were noted in three (15.7%). 12 (63.1%) had GFR <60 ml/min at their presentation in Table 6.

Of the nine patients presented with nephrotic syndrome, all were started with angiotensin-converting enzyme inhibitor titrated to reduce the blood pressure target of 125/75 mm Hg, eight were started with steroids. Four (50%) had partial remission. 1 (12.5%) had complete remission. 3 (37.5%) never

Table 4: IF finding

IF finding	*n* (%)
IgA+C3	13 (48.1)
IgA+C3+IgM	10 (37.3)
IgA+C3+IgM+IgG	4 (14.8)
IgA+C3+IgM+C1q	2 (7.4)

IF: Immunofluorescence

Table 5: Variables determining renal failure at presentation

Variables	Renal failure at presentation *n*=18 patients
Mean age	27.9 years
Sex - M:F (%)	72:28
Hypertension (%)	61
Macrohematuria (%)	38
PCR>3 g (%)	44
M0 (%)	17
M1 (%)	83
E0 (%)	44
E1 (%)	56
S0 (%)	51
S1 (%)	50
T0 (%)	5.5
T1 (%)	44
T2 (%)	50
Crescents (%)	22.2
Vascular thickening (%)	22.2

Table 6: Variables analyzed in the progression of CKD

Variables	Progressed to CKD *n*=8	Normal renal function at the end of follow up *n*=19	*P* value
Mean age	32.6	28	No significance
Sex - M:F (%)	64:36	60:40	No significance
Hypertension (%)	63	42	0.98
Macrohematuria (%)	63	47.3	
Response to proteinuria CR (%)	12.5	47.1	0.0001
Partial response (%)	50	36.8	
No response (%)	37.5	15.7	
M1 (%)	75	68.4	0.8
E1 (%)	62.5	47	0.344
S1 (%)	62.5	42	0.001
T0 (%)	12.5	31.5	0.07
T1 (%)	50	42.1	
T2 (%)	50	26.3	
Crescents (%)	25	15.7	0.2192
GFR <60 ml/min at present (%)	87.5	63.1	0.04
Vessel wall thickening (%)	37.5	26.3	0.29

CKD: Chronic kidney disease

Table 7: Comparison of clinical presentation and syndrome

Variables	Chandrika *et al.*[12]	Mittal *et al.*[10]	Muthukumar *et al.*[11]	Present study
Mean age years	30	29.9	25.7	27.3
M:F	1.5:1	3:1	2:1	1.7:1
Mean serum creatinine	2.2	3.1	-	2.03
Hematuria (%)	49.3	78.8	54.9	64
Hypertension (%)	49	81	30	59.3
Nephrotic syndrome (%)	36.7	23.1	25.5	33
RPGN (%)	-	-	21.4	14.8
AKI (%)	11	-	4.1	7.4

RPGN: Rapidly progressive glomerulonephritis, AKI: Acute kidney injury

Table 8: MEST scoring in various studies

Variables	Cattran *et al.*[13]	Mittal *et al.*[10]	Nasri *et al.*[14]	Our study
Endocapillary score (E1) (%)	42	24.4	32	51.8
Sclerosis score (S1) (%)	76	48.6	62	40.7
Tubular atrophy/interstitial fibrosis score in (T1 and T2) (%)	88	73.96	80	81.7

attained remission. 3 patients who attained complete remission retained their renal function. Of the five who had partial and nil remission, three patients progressed to CKD.

Of the 4 patients presented with rapidly proliferative glomerulonephritis, steroid and cyclophosphamide was given in as per vasculitis protocol. Half of them progressed to CKD, half were not. AKI was noted in 2 patients. One had crescent and one with no discernible findings.

DISCUSSION

Of the 27 biopsy proven IgAN, 17 were male. Male:Female ratio in our study was 1.7:1 which was comparable to Chaco *et al.*,[2] with M:F ratio 1.85:1. Mean age at presentation in our study was 27.3 years compared to Mittal *et al.* had a mean age of 29.9 years,[10] and Muthukumar *et al.*[11] showed mean age of 25.7 years but a decade younger than that quoted in the western world. The majority were in 10-29 years (66%).

11 (40.7%) patients presented with the macrohematuria. Chandrika *et al.*, documented 49.3% had the same.[12] Hypertension was noted in 16 patients (59.3%). Hypertensive retinopathy was noted in 7 patients (25.9%). Muthukumar *et al.* documented 21.4% had malignant hypertension.

Chandrika *et al.* documented 36.7%. Muthukumar *et al.* documented 25.5% had nephrotic syndrome. Mittal *et al.* study showed 23.1% had nephrotic syndrome.[12] In our study, 33% had nephrotic syndrome. RPGN was noted in 14.8% patients. Muthukumar *et al.* documented 21% with RPGN. AKI was present in 7.4% patients compared to Muthukumar *et al.* (Table 7).[11]

Renal biopsy results of the 27 patients revealed mesangial hypercellularity (M score >0.5) in 70.3%. Endocapillary proliferation was noted in 51.8%. Sclerosis score (S1) was noted in 40.8%. Tubular atrophy/interstitial fibrosis score (T1 and T2) was37.3% and 44.4% (Table 8). In our study, arterial score was 25.9%.

Immunofluorescence study of renal biopsy tissue in our study showed IgA + C3 present in 13 (48.1%), IgA + C3 + IgM in 10 (37.3%), IgA + C3 + IgM + IgG in 4 (14.8%), and IgA + C3 + IgM + C1q in 2 (7.4%). Chandrika *et al.* showed IgA + C3 present in 105 (46.25%), IgA + C3 + IgM in 80 (35.24%), IgA + C3 + IgM + Immunoglobulin G in 20 (8.82%) and IgA + C3 + IgM + C1q in 5 patients (2.20%). In their study, full house pattern was noted in 4 (1.76%), but not in our study.

In our study, renal failure at presentation (GFR <60 ml/min) was noted in 18 (66.6%). Muthukumar *et al.* showed 61% had renal failure at diagnosis.[11] The mean age was 27.9 years in who presented with renal failure at diagnosis. 13 (72%) patients were male, which was comparable to Muthukumar *et al.* (70%). Hypertension was noted in 11 (61%). Macrohematuria was noted in 7 (38%), the nephrotic range of proteinuria was present in 8 (44%).

Of the 18 patients who presented with renal failure at presentation, 83% had the mesangial score (M >0.5), 44% had Endocapillary proliferation, and 50% had sclerosis score (S1).Tubular atrophy/interstitial fibrosis score (T1 and T2) was noted in 44.4% and 51.1%, respectively. Crescents were noted in 22% of the above cohort. Muthukumar *et al.* showed interstitial fibrosis in 90% of patients and crescents in 16.7%.[11]

The bivariate variables were analyzed using Chi-square fisher's exact test. The multivariable was analyzed by multiple regressions. Male sex, mean age both had

no significant correlation in those with renal failure at presentation. Hypertension, macrohematuria, and proteinuria >3 g/day were had no significant correlation in this cohort. Mesangial hypercellularity (M score >0.5), tubular atrophy/interstitial fibrosis score (T1 and T2), were significantly associated with renal failure at presentation. Crescents had no significant statistical association. There is no statistical association between vessel wall thickening and those with renal failure at presentation.

Muthukumar *et al.* showed that there were no significant correlation between male, hypertension, macrohematuria, and proteinuria >3 g/day in those who presented with renal failure at presentation. They showed interstitial fibrosis, vessel wall thickening were associated with renal failure at presentation. By multivariate analysis they showed only interstitial fibrosis was associated with renal failure at presentation, but not vessel wall thickening. Treatment response in nephrotic syndrome.[11]

In our study, 33% presented with nephrotic syndrome all of them are started with angiotensin-converting enzyme inhibitors, and BP was titrated to 120/75 mmHg. Steroid was started in eight of them, 1 (12.5%) attained complete remission, 4(50%) had partial remission, and 3 (37.5%) had no remission. Seven patients with partial and nil remission, five of them progressed to renal failure, two were not, but statistically not significant ($P = 0.54$). Reich *et al.* showed those who had sustained proteinuria >3 g/day had 25-fold faster declines in renal function.

In our study during follow-up period, 8 patients (29.6%) progressed to CKD. Mean age was 32.6 years. 63% of them had macrohematuria. Hypertension persisted in five (63%). There is no statistical significance noted for hypertension and macrohematuria. Those progressed to CKD three (37.5%) had proteinuria >3 g/day (nil remission), four (50%) had proteinuria in the range of 0.3-3 g/day (partial remission), one (12.5%) had urinary protein of <0.3 g/day. There was statistical significance noted for who had no response to the reduction in proteinuria with that progressed to CKD.

There was no statistical significance noted for the mesangial score (M1) in 75% and endocapillary proliferation 62.5% of patients in those who progressed to CKD. Segmental score (S1) was noted in 62.5% who progressed to CKD, which was statistically significant. Tubular atrophy/interstitial fibrosis score (T1 and T2) was noted in 50% of each who had progressed to CKD, which was not statistically significant. 28% had crescents which were not statistically significant. There is no statistical association between vascular wall thickening and CKD progression.

CONCLUSION

Nephrotic syndrome is the most common clinical presentation in IgAN. The majority presented with renal failure at entry into the study. Severe MEST scoring was significantly associated with renal failure at presentation. Non-responders of proteinuria and those who had severe S in MEST scoring system progressed to CKD. Crescents had no statistical association for progression to CKD. Complete or partial remission of proteinuria had less chance for the progression to CKD.

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