

IgA NEPHROPATHY – ITS SEASONAL VARIATION AND CLINICO PATHOLOGICAL PROFILE IN LOCAL PATIENTS

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ABSTRACT

Objective: To study the frequency of IgA nephropathy in relation to seasonal variation and its clinico-pathological profile at Military Hospital Rawalpindi.

Study Design: A descriptive study.

Place and Duration of Study: Military Hospital, Rawalpindi, Pakistan from Jan 2010 to Mar 2012

Patients and Methods: The study was conducted at Military Hospital Rawalpindi on 289 consecutive renal biopsy specimens. Ultrasound guided percutaneous renal biopsies were carried out in patients with the following findings: 1) Proteinuria > 1000 mg/day in adults, 2) Isolated glomerular haematuria with proteinuria 500 – 1000 mg/day, 3) Proteinuria < 500 mg/day with impaired renal functions, 4) Steroid resistant nephrotic syndrome in children. Light microscopy after Haematoxylin & Eosin, PAS and Silver stains was employed for diagnosis on formaline fixed tissue, while diagnosis of IgA nephropathy was established upon findings of characteristic IgA deposits on immunofluorescence studies on a separate core of unfixed tissue.

Results: A total of 289 renal biopsies were performed, out of which 45 were diagnosed with IgA nephropathy indicating a frequency of 15.5 %. The most common mode of clinical presentation was asymptomatic microscopic haematuria with proteinuria 500 – 1000 mg per day in 14 patients (31%). The most common histopathological finding was mesangial proliferation and hypercellularity in 15 biopsies (43%). Deposition of IgA with IgM and C3 complement was the most frequent finding on immunofluorescence in 37 biopsies (82.2%). About 80% of patients with IgA nephropathy presented in relatively colder months starting from Jan – Mar and from Sep – Dec.

Conclusion: IgA nephropathy is one of the most frequent diagnoses on renal biopsies. It usually presents in young male adults in the age range of 21–30 years with most common clinical presentation being asymptomatic microscopic haematuria. The most common pathological finding was mesangial proliferation and hypercellularity with deposition of IgA with IgM and C3 complement. Presentation of patients in colder months is possibly related to upper respiratory tract infections.

Keywords: Glomerulonephritis, IgA Nephropathy, Immunofluorescence

INTRODUCTION

IgA nephropathy is the most common lesion found to cause primary glomerulonephritis worldwide¹. There is a male to female ratio ranging from less than 2:1 in Japan to as high as 6:1 in Northern Europe and the United States. In addition, whites and Asians are more prone to IgA nephropathy than blacks²⁻⁴. In a Chinese study of 13, 519 renal biopsies, IgA nephropathy constituted 45 percent of all cases of primary glomerulonephritis³. However, IgA deposits may also be seen on kidney biopsy in individuals with

no evidence of renal disease. The reported incidence of mesangial IgA deposition in apparently healthy individuals ranges from 3 to 16%⁵.

Although IgA nephropathy is considered a sporadic disease, there may be a genetic predisposition. Among affected families, the disease appears to be transmitted as an autosomal dominant trait with incomplete penetrance. An infectious source has long been suspected, and there have been occasional reports of IgA nephropathy in association with bacterial and viral infections. None, however, has been consistently implicated by the finding of microbial antigen in glomerular deposits in typical cases of IgA nephropathy. Food antigens have also been proposed (particularly gliadin),

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but their involvement is not proven. A severe form of IgA nephropathy, which may be crescentic, has been reported in association with severe staphylococcal infection⁶.

The presence of IgA nephropathy is established only by kidney biopsy. The pathognomonic finding is observed on immunofluorescence microscopy, which demonstrates prominent, globular deposits of IgA (often accompanied by C3, IgM and IgG) in the mesangium and, to a lesser degree, along the glomerular capillary wall². Mesangial deposition of secretory IgA has also been observed, although the pathogenic significance of this is unknown.

The major finding on light microscopy is focal or more often diffuse mesangial proliferation and matrix expansion. Segmental crescents are relatively common. There is usually little or no glomerulosclerosis, a manifestation of chronic disease, on initial biopsy. Patients may eventually develop glomerulosclerosis, by which time they have decreased glomerular filtration rate (GFR) and increased proteinuria⁷.

Approximately 40 to 50% present with one or recurrent episodes of visible hematuria, usually following an upper respiratory infection. Another 30 to 40% have microscopic hematuria and usually mild proteinuria, and are incidentally detected on a routine examination. Gross hematuria will eventually occur in 20 to 25% of these patients. Less than 10% present with either nephrotic syndrome or acute rapidly progressive glomerulonephritis. Rarely, IgA nephropathy may present with malignant hypertension⁸⁻¹⁰.

Keeping in view the heterogeneous presentation of IgA nephropathy and its predisposition in young males, the study was planned to find out the clinico-pathological profile of the patients suffering from IgA nephropathy in local patients.

PATIENTS AND METHODS

The study was conducted at Military Hospital Rawalpindi from Jan 2010 to Mar 2012 on 289 consecutive renal biopsy specimens. Ultrasound guided percutaneous renal biopsies

were carried out in patients with the following findings:

1. Proteinuria > 1000 mg/day in adults
2. Isolated glomerular haematuria with proteinuria 500 – 1000 mg/day
3. Proteinuria < 500 mg/day with impaired

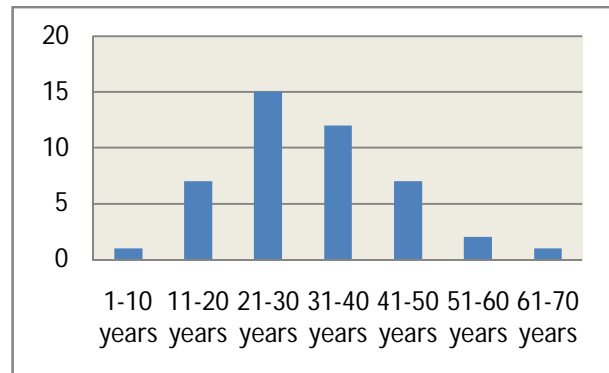


Figure-1: Age distribution of patients with IgA nephropathy (n = 45).

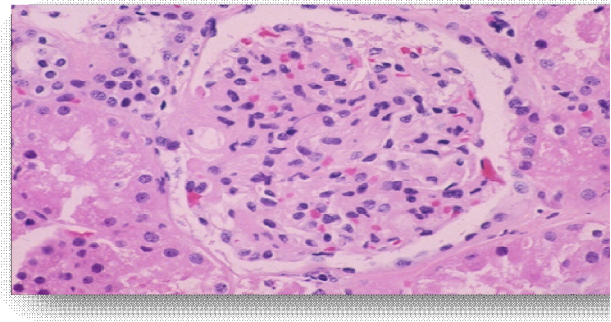


Figure-2: Photomicrograph of mesangial proliferative glomerulonephritis (H & E Stain x200)

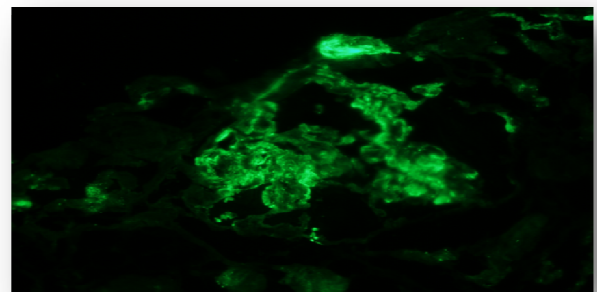


Figure-3: Direct immunofluorescence microscopy showing mesangial IgA deposits.

renal functions

4. Steroid resistant nephrotic syndrome in children

An informed written consent was obtained from all patients undergoing kidney biopsy for various indications. All patients were tested for full blood count, renal functions, prothrombin time (PT), partial thromboplastin time with kaolin (PTTK) and bleeding time (BT). Blood pressure was controlled (BP < 140/90 mm Hg), anemia corrected (Hemoglobin was brought up to 10 mg/dl) and coagulation profile corrected using vitamin K or rarely fresh frozen plasma, when required, before subjecting the patients for kidney biopsy. Biopsy was performed in prone position. The lower pole of the left kidney was located in the majority of subjects except in those where there was a cyst at the lower pole of the left kidney, then the caudal pole of the right kidney was located with ultrasound. Kidney biopsy was performed with automated disposable gun (Monopty Bard U.K®) under local anesthesia (2% Xylocaine) and under ultra sound guidance. Patients with deranged coagulation profile, uncontrolled hypertension (systolic BP >160 mmHg & diastolic BP >100 mm Hg), hypotension (BP < 100/60 mm Hg), anaemia (Hb < 10 mg/dl according to international guidelines), evidence of malignancy, evidence of congenital anomalies of kidneys on ultrasound, skin disorders / local infection affecting the skin overlying biopsy site and unwillingness for renal biopsy were excluded.

Minimally two cores of renal tissue were obtained and sent for light microscopy in 10% formalin and immunofluorescence in 0.9% normal saline to Armed Forces Institute of Pathology (AFIP). For direct immunofluorescence, tissues were stained with fluorescein isothiocyanate (FITC) labeled antibodies against IgG, IgA, IgM, C3, C4 and fibrinogen. For histopathological examination, biopsies were fixed in 10% formalin and stained with hematoxylin and eosin, periodic acid schiff and methanamine silver stains, if required, for microscopy.

The baseline demographics, clinical data along with routine urine examination, and biochemical parameters at the time of presentation/biopsy were also analyzed. Normal renal function was defined as GFR \geq 90 ml/min/1.73 m² body surface area, estimated using the Cockcroft-Gault formula. The definition of hematuria was > 2 RBCs per high-power field in the urinary sediment. Nephrotic syndrome was defined as proteinuria > 3.5 g/day/1.73 m² Body surface area with hypoalbuminemia, edema, and hyperlipidemia. Nephritic syndrome was defined as hematuria (usually with dysmorphic RBCs/ RBC casts) with proteinuria < 3.0 g/day, hypertension, and elevated serum creatinine. Chronic kidney disease was defined as severe irreversible kidney damage and serum creatinine levels persistently above 1.5 mg/dl for more than three months⁸. The data was analysed on SPSS version 13.0.

RESULTS

Out of 289 renal biopsies performed, 45 were identified as IgA nephropathy (15.5%) primarily on Immunofluorescence studies. The mean age was 29.4 years (range 10-65 years). These included 37 males (82 %) and 08 females (18%) with male to female ratio of 4:1. The most common age group affected was 21 – 30 years 15 cases (33%) followed by 31 – 40 years 12 cases (26.6%) (Fig.1). Out of total 48 identified as IgA nephropathy, three cases that had IgA deposition on immunofluorescence, two were diagnosed as Henoch Schonlein Purpura and one was diagnosed as Alport syndrome, were excluded from the study.

The most common mode of presentation was asymptomatic microscopic haematuria with proteinuria 500 – 1000 mg per day in 14 (31%) cases followed by episodic gross haematuria with subnephrotic proteinuria in 11 (24%) and nephrotic syndrome in 11 (24%) of cases. Rapidly progressive glomerulonephritis was the least common presentation in 9 (20%) of cases (Table-1).

The most common histopathological presentation was mesangial proliferation and

hypercellularity in 15 (43%) followed by diffuse immunofluorescence (Fig-3). Deposition of IgA mesangioproliferative glomerulonephritis with IgG and C3 complement was noted in 20

Table-1: Comparative frequency of mode of presentation.

	Features	Number (%) (n = 45) Current Study	Number (%) (n = 30) (Hamid et al)	Number (%) (n = 10) (Muzaffar et al)
1	Asymptomatic microscopic haematuria proteinuria 500 – 1000 mg	14 (31 %)	4 (13 %)	4 (40 %)
2	Episodic gross haematuria subnephrotic proteinuria	11 (24 %)	8 (27 %)	2 (20 %)
3	Nephrotic syndrome	11 (24 %)	11 (37 %)	4 (40 %)
4	Non nephrotic proteinuria	-	4 (13%)	-
5	Rapidly progressive glomerulonephritis	9 (20 %)	-	-

Table-2: Comparative frequency of histopathological findings.

	Features	Number (%) n = 35 (Current Study)	Number (%) n = 39 (Hamid et al)	Number (%) n = 10 (Muzaffar et al)
1	Mesangial proliferation and hypercellularity	15 (43%)	7 (35 %)	-
2	Diffuse mesangio proliferative glomerulonephritis with focal sclerosis	10 (28.5%)	-	3 (33.3 %)
3	Rapidly progressive crescentic glomerulonephritis	8 (23%)	3 (15 %)	-
4	Membrano proliferative glomerulonephritis	2 (5.7%)	4 (20%)	-
	focal segmental glomerulosclerosis	-	-	2 (22.2 %)
	minimum histology lesion	-	-	2(22.2 %)
	Advanced chronic glomerulonephritis	-	-	2 (22.2 %)
5	Non diagnostic / insufficient Tissue/rejection	3 (8.5 %)	5 (25%)	1 (10%)
6	Misssing	7 (20 %)	19 (48.7%)	-

focal sclerosis in 10 (28.5%) (fig-2). This was followed by rapidly progressive crescentic glomerulonephritis in 8 (23%) and membranoproliferative glomerulonephritis in 2 cases (5.7%). Out of 45 biopsies, 10 were excluded because of insufficient or inadequate samples (Table-2).

Deposition of IgA with IgM and C3 complement in the mesangial region of glomeruli was the most frequent finding in 37 (82.2%) of

(44.4%) biopsies. Deposition of IgA with both IgG and IgM with C3 was seen in 22 (48.8%) biopsies. IgA with IgG or IgM without C3 was noted in 8 (17.7%) of biopsies (Table-3).

An important aspect seen in this study was occurrence of cases in relation to cold weather. Nineteen (42%) cases occurred from Jan to Mar, five (11%) cases occurred from Apr to Aug and 21 (46.6%) cases occurred from Sep to Dec.

DISCUSSION

IgA nephropathy is the most common cause of primary (idiopathic) glomerulonephritis worldwide¹⁻⁴. Its prevalence varies in different parts of the world ranging from 2-52% of all renal biopsies. The variation shows a geographic pattern, as 5% to 10% frequency was reported

prevalence of IgA nephropathy in 39 patients (10.4%) out of 376 renal biopsies received for immunofluorescent studies in 2011²³.

Our study showed a frequency of IgA nephropathy of 15.5%. The apparent increase in percentage of IgA nephropathy may be due to an increase in the number of patients undergoing

Table-3: Comparative frequency of immune deposits detected on immunofluorescence studies in patients with IgA nephropathy.

	Features	Number (%) n = 45 (Current Study)	Number (%) n = 39 (Hamid et al)	Number (%) n = 10 (Muzaffar et al)
1	IgA + IgM + C3	37 (82.2 %)	-	-
2	IgA + IgG + C3	20 (44.4 %)	-	-
3	IgA + IgM + IgG + C3	22 (48.8 %)	28 (71.8 %)	-
4	IgA + IgM/IgG	8 (17.7 %)	5 (12.8 %)	3 (30 %)
5	IgA + C3	-	4	5 (50 %)
6	IgA	-	2	2 (20 %)

from North America, United Kingdom, and northwestern Europe, 20% to 35% in most European studies and 25% to 52% in studies from Asian countries¹¹. The highest prevalence in Asia was reported from Singapore and Japan¹². In our region, it is reported to be 7.8% and 14.26% in India¹³, 11.9% in Bangladesh¹⁴ and 10.2% in Saudi Arabia¹⁵.

In Pakistan, its prevalence was initially reported to be 2% in a study published in 1988 by Khan et al¹⁶, in which 50 cases of renal biopsies were studied by immunoperoxidase method. Subsequently, the same author reported a series of 102 renal biopsies in 1990, in which IgA nephropathy was observed in 5.9% of the biopsies¹⁷. Thereafter, Lakhnana et al reported a prevalence of 7.9% of 238 cases of glomerulopathies from the northern part of the country¹⁸.

Muzaffar et al reported a prevalence of 12.65% from southern part of the country and Noor et al reported a prevalence of 20.83% from Khyber Pakhtunkhwa province^{19,20}. More recently a prevalence of IgA nephropathy at a rate of 2.5% and 1.1% in adults and children respectively was reported, presenting with nephrotic syndrome by Kazi and Mubarak et al^{21,22}. Tipu et al reported a

renal biopsy owing to low threshold for renal biopsy in our setup. In earlier studies renal biopsies were not performed for microscopic hematuria and proteinuria 500 – 1000 mg per day.

IgA nephropathy has been reported in all age groups with peak incidence in the second and third decade of life with male preponderance¹. A similar pattern was observed in our study with a mean age of 29.4 years and a male predominance of 4:1 which is consistent with international findings (2:1 in Japan to 6:1 in Europe and United States)¹, although smaller ratios (approx 1.2:1) have been reported in regional studies^{14,18}. In addition, we calculated its frequency in various age groups and found that young people are at increased risk of the disease similar results were obtained in international studies, reporting its highest incidence in the second and the third decades of life¹.

The most common mode of presentation in our study was asymptomatic microscopic haematuria with proteinuria 500 – 1000 mg per day in 14 (31%) cases followed by an equal presentation of episodic gross haematuria with subnephrotic proteinuria 11 (24%) and nephrotic syndrome 11 (24%). Rapidly progressive

glomerulonephritis was the least common presentation 9 (20%). Nephrotic syndrome was shown to be the major clinical presentation by Hamid et al to 38% followed by hematuria and proteinuria 27%²³. Same clinical pattern was described by Muzaffar et al to be 40%¹⁹. Similarly, nephrotic range proteinuria has been shown to be the most common presentation in India as well by Chacko and Siddappa^{24,25}. This difference in mode of presentation may be due to a difference in selection criteria for renal biopsy.

The most common histopathological lesion associated with IgA nephropathy worldwide is focal or diffuse expansion of mesangial regions, with cells and matrix. In our study the most common histopathological presentation was mesangial proliferation with hypercellularity in 15 (43%) of biopsies and diffuse mesangioproliferative glomerulonephritis with focal sclerosis in 10 (28.5%) of biopsy samples, both lesions constituting 70% of renal biopsies. Out of 45 biopsies, 10 were excluded because of insufficient or inadequate samples. The findings were consistent with the findings reported by Tipu et al and other local studies.

An important aspect seen in this study was occurrence of cases in cold weather. Nineteen (42%) cases occurred from Jan to Mar, five (11%) cases occurred from Apr to Aug and 21 (46.6%) cases occurred from Sep to Dec. This may be due to relatively frequent occurrence of common cold and upper respiratory tract infections particularly in changing weather conditions and dry atmosphere.

CONCLUSION

IgA nephropathy is one of the most frequent diagnosis in renal biopsies. It usually presents in young male adults in the second decade of life with asymptomatic microscopic haematuria being the most common clinical presentation. The most common pathological finding was mesangial proliferation and hypercellularity with deposition of IgA with IgM and C3 complement. Presentation of patients in colder months is possibly related to upper respiratory tract infections.

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