ORIGINAL ARTICLE

Prevalence of IgA Nephropathy: A 10 Years' Experience from Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Muhammad Ali, Shafique Ahmed, Ayesha Ejaz, Ghazala Usman, Abdul Manan Junejo, Hina Iram, Moiz Ahmed
Jinnah Postgraduate Medical Center, Jinnah Sindh Medical University, Karachi, Pakistan.

ABSTRACT

Background: Immunoglobulin A (IgA) is considered the most frequently dealt primary glomerulonephritis, worldwide. The Berger's disease or IgA nephropathy is a mesangial proliferative glomerulonephritis characterized by deposition of immunoglobulin A in kidneys. The aim of the study was to report the prevalence of IgA nephropathy and the associated parameters (age, gender, and body mass index) in our population.

Methods: This was a retrospective study, accomplished at Jinnah Postgraduate Medical Centre, Karachi, Pakistan, from June 2009-May 2019. The histopathology and immunofluorescence of renal biopsies of 519 patients were studied and the prevalence of biopsy proven IgA nephropathy was determined. The Chi-square test was used for association of biopsy proven IgA nephropathy with age, gender, and body mass index. A *p*-value of 0.05 or less was considered statistically significant.

Results: A total of 519 biopsies were studied, out of those, only 4 (0.8%) had IgA nephropathy with male dominance in the last 10 years at Karachi, Pakistan. Male to female ratio was found to be 3:1. The most common clinical indication for renal biopsy was isolated hematuria in 50% of the cases followed by acute kidney injury and nephritic syndrome with 25% each respectively. Most of the patients suffering from proteinuria (> 3.5gm/24 hours), microscopic hematuria in 80% cases, high blood pressure in 50% cases, with other associated symptoms including edema, gastrointestinal, and skin-related symptoms reported.

Conclusion: Immunoglobulin A (IgA) nephropathy is not a commonly diagnosed glomerular lesion. Further large-scale cohorts can aid in determining the other factors associated with a low frequency of IgA nephropathy.

Keywords: Biopsy; Glomerulonephritis; Immunoglobulin A; Nephropathy.

Corresponding Author:
Dr. Ghazala Usman
Jinnah Postgraduate Medical Center,
Jinnah Sindh Medical University, Karachi, Pakistan.
Email: ghazala.usman@jsmu.edu.pk
doi.org/10.36283/PJMD9-4/003

INTRODUCTION

Immunoglobulin A (IgA) nephropathy is relatively a new recognized disease. Jean Berger and Hinglas first described it in their seminal papers in 1968[1-2]. Much about the disease is studied but the exact pathogenic mechanism remains unclear[3]. IgA is the most frequently dealt primary glomerulonephritis (GN), worldwide[4]. It is also known as Berger's disease and is a mesangial proliferative GN characterized by deposition of immunoglobulin A in kidneys. The estimated frequency of IgA nephropathy is 2.5 cases per 1million adults per year[5]. There has been geographical variation associated with presence of gene alleles, which protect against the IgA nephropathy (IgAN) [6]. Almost all the studies show male predominance with 2:1 ratio and found more in white population[7-8]. Prevalence appears highest in Asian countries like Singapore, Japan, Australia and the European countries with percentages of 20-40%. In the United States of America, Canada and the United Kingdom, prevalence appears to be as low as 2-10% except in American Indians where 38% prevalence is observed[9].

Renal biopsy for histopathology remains the gold standard technique for the diagnosis, prediction of clinical course and outcome of the renal diseases[10]. The light microscopic changes of IgAN vary from minor changes to crescentic GN. Typical characteristics of IgA nephropathy are diagnosed using different laboratory tests including the light and electron microscopy and immunofluorescence tests. The most common changes associated with this disease are focal and generalized expansion of the basement membrane on light microscopy, the deposition of Immunoglobulin A on Immunofluorescence studies within mesangial regions with focal para-mesangial and subendothelial extension. Clinically, most of the patients are asymptomatic and unaware of the problem. In these patients, Immunoglobulin A Glomerulonephropathy is only diagnosed incidentally during the screening for other diseases. However, in certain cases, the disease is associated with aggressive clinical courses and up to 20% of the patients present with severe azotemia.

Few recognized features of this disease are microscopic hematuria and asymptomatic proteinuria, episodes of macro hematuria overlapping with the infection of upper respiratory tract, loin pain, and abnormal sediments in urine[11]. Prognosis of the disease varies with the frequency of chronic kidney failure (CKD) and end stage renal diseases (ESRD) having 30-35% cases whereas, ten-year renal survival of up to 90% cases[12]. According to the histopathological criteria, the poor prognostic factors are the presence of glomerular sclerosis, glomerular capillary wall invasion, and interstitial fibrosis[11]. As the IgA nephropathy has indolent course, around 30% of the patient's progress to ESRD in 20 years, particularly who present with heavy proteinuria, hypertension, and renal insufficiency. The primary aim of this study was to report the prevalence of IgA nephropathy based on histopathology and immunofluorescence in the last ten years among the patients admitted at a tertiary care center.

METHODS

This was a retrospective analysis of all the consecutive percutaneous kidney biopsy of native and some transplanted kidneys, performed at the Department of Nephrology from 1st January 2009 to 30th October 2019 for a duration of 10 months. The ethical approval was obtained from the ethical committee of the institutional review board prior to the study with a reference no F.2-18/2019-GEN/37670-A/JPMC. A total of 519 renal biopsy reports of varied age groups were collected, studied, and enrolled in the present study.

Renal tissue from all patients with suspected nephropathy, kidney injury, proteinuria, and hematuria were sent for histopathological analysis. Comorbidities were classified as Diabetes Mellitus (DM) and hypertension (HTN). The biopsy procedure was done after informed written consent was obtained from all participants. Biochemical parameters like hemoglobin (HB)>10g/dl, Platelets >100000/l, prothrombin time (PT)/INR <1.2 times of control, activated partial thromboplastin time (aPTT) <1.2 times of control, urea <50mg/dl and sterile urine were observed. Desmopressin acetate (DDAVP) 0.4ug/kg was given 2-3 hours prior to renal biopsy to the patient whose urea was >50mg/dl. Ultrasound Kidneys was also a prerequisite in order to check the size of the kidney, cortical thickness, parenchymal changes and pelvicalyceal system. On the day of procedure, blood pressure (BP) >140/100mmHg was an absolute indication to delay or postpone the procedure. The procedure was defined to the patient before proceeding. The patient had to lie in a prone position during the procedure in native kidney, while supine in case of a transplanted kidney.

Two core samples were taken during the procedure. After the completion of procedure, the patients were advised to have bed rest in supine position at least for 30 to 60 minutes and their vitals including BP was checked as per protocol of the hospital to avoid the hypotensive crisis or shock. Beside this, the color of urine was observed for presence of evident hematuria. The patients were cleared 8-12 hours post-procedure if they were stable and no macroscopic hematuria was detected. The patients were advised for bed rest for next 24 hours and to avoid physical activities for next 24-48 hours. Biopsies were conducted with Bard®Monopty® disposable core biopsy instrument of 16 and 18 gauge. Two core samples were taken for light microscopy and immunofluorescence. The histopathologist prepared tissue sectioning and paraffin embedding. These entire specimens were analyzed by microscopy using Hematoxylin and Eosin, Periodic Acid Schiff, Jones Silver Methenamine, Congo Red and Gomori Trichrome Stain. Immunofluorescence studies were performed using anti human immunoglobulin, protein C complements, Kappa and Lambda light chains.

The diagnosis of biopsy proven renal disease was made as per standard diagnostic criteria for each disease. The statistical analysis was done using Microsoft excel and statistical package for the Social Sciences (SPSS) version 24.0. The quantifiable variables (age) have been described as mean± standard deviation (SD). The prevalence of biopsy-proven IgA nephropathy was presented as frequency and percentages. The Chi-square test was used to determine the frequency of biopsy proven IgA nephropathy among different age, gender, and body mass index.

 doi.org/10.36283/PJMD9-4/003

RESULTS

Immunoglobulin (IgA) nephropathy was found in 4 (0.8%) cases out of 519 with male predominance in the last 10 years at JPMC, Karachi, Pakistan. The males were evidently predominant with a ratio of 3:1 and with the mean age (Table 1) of 22±2 years. In the present study, the 0.8% prevalence of IgA nephropathy was observed.

Table 1: The descriptive characteristics of study population.

Variable	Mean ± SD
Age (years)	22±2
Mean Height (m)	1.63 ± 1.61
Mean Weight (kg)	45.54± 6.7
Mean body mass index (BMI)(kg/m)^2	22.6± 2.4

The most frequent indications for the kidney biopsy was isolated hematuria (Figure 1) in 259 (50%) of the cases followed by acute kidney injury and nephritic syndrome with 130 (25%) each respectively.

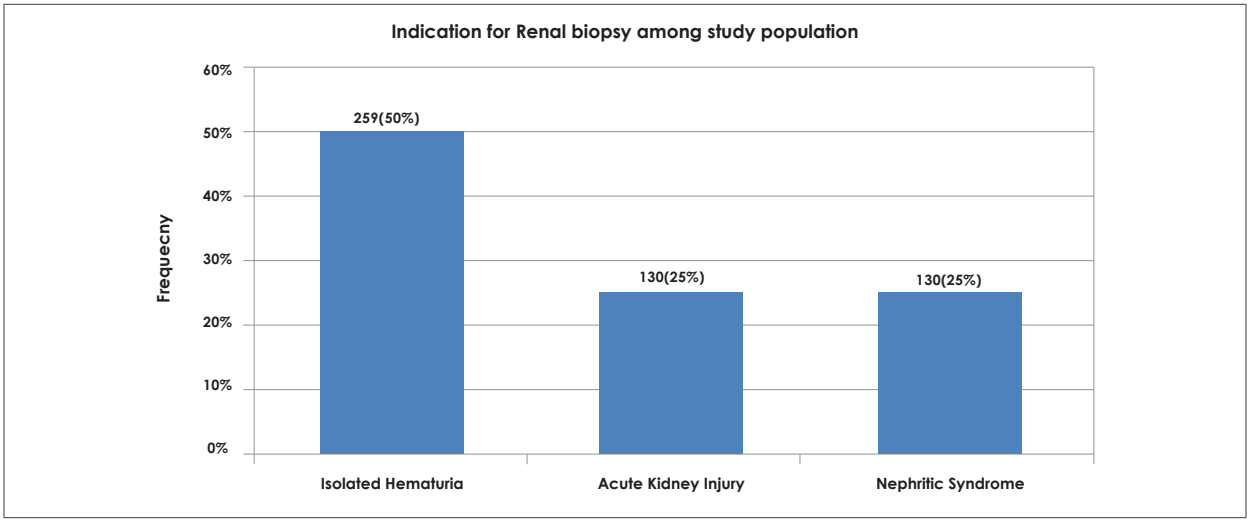

Figure 1: Indication for renal biopsy among study population.

The study revealed and compared the patients who were diagnosed with other kidney related illnesses and showed patients with IgA nephropathy were more likely to be 15 years or older and had a significantly lower body mass index with a *p*-value of 0.002 and <0.001 respectively. However, gender (Table 2) had no significant difference in either group.

Table 2: Association of independent variables with the incidence of immunoglobulin (IgA) nephropathy.

Variables	IgA	Other Kidney Diseases	*p*-Value
Age (years)			
<10 years	1 (25%)	203 (39.4%)	0.002
10-15 years	2 (50%)	269 (52.2%)	
>15 years	1 (25%)	40 (7.8%)	
Gender			
Male	3 (75%)	365 (70.9%)	0.514
Female	1 (25%)	150 (29.1%)	
Body Mass Index			
Underweight (< 18.5)	1 (25%)	59 (11.5%)	<0.001
Normal Weight (18.5 – 24.9)	3 (75%)	347 (67.5%)	
Overweight (>25)	0	109 (21.2%)	

The study also explored the histopathological features of IgA nephropathy according to the Haas Grading system12. Out of the four cases that were confirmed as IgA nephropathy, one case showed diffuse proliferative glomerulonephritis with IgA depositions, two cases showed minimal histological lesion with IgA and C3 deposition, while the fourth case showed crescentic glomerulonephritis.

The clinical characteristics (Table 3) of patients diagnosed with IgA nephropathy with the majority of the patients suffering from proteinuria > 3.5gm/24 hours, microscopic hematuria in 3 (80%) cases, high blood pressure in 2 (50%), and other associated symptoms including edema, gastrointestinal, and skin-related symptoms.

Table 3: Clinical characteristics of patients with immunoglobulin (IgA) nephropathy.

Case Number	Proteinuria (gm/24 hours)	Hematuria	High Blood Pressure	Other symptoms
1	> 3.5	Microscopic	Positive	Edema, CRF
2	>3.5	Macroscopic	Negative	Failure to thrive
3	1-2	Microscopic	Negative	Abdominal pain, cramps
4	>3.5	Microscopic	Positive	Fever, pain, skin rash

DISCUSSION

Prevalence of kidney diseases has increased over the previous few decades and has put a huge burden on the health care sector around the world. Lack of awareness of delayed diagnosis, non-availability of trained renal physicians, staff, and lack of treatment facilities in the developing world lead to increased number of patients of chronic kidney disease that needs either dialysis or renal transplantation[10].

Kidney diseases consist of a wide variety of causes and histopathological lesions. Glomerular diseases are one of the commonest causes that if detected and treated at initial stages properly help to prevent the patients from developing chronic kidney disease. Glomerular diseases can be either primary or secondary, among them IgA Nephropathy is one of the common diseases in countries where renal biopsies are performed frequently. Its estimated frequency is at least 2.5 cases per year per 100000 adults[12]. It is less common in black population. However, its prevalence is widely either underestimated or overestimated. Prevalence is different in different races, regions as well in countries where screening is done in routine for school going children. Percutaneous renal biopsy for histopathology and Immunofluorescence is the gold standard tool for the diagnosis, prediction of clinical course and outcome for the variety of renal lesions.

Immunoglobulin (IgA) nephropathy has different mode of presentation, either detected only on routine investigations or can present with presence of gross blood in urine, Nephropathy including the nephritic syndrome or glomerulonephritis. We analyzed the 519 renal biopsies of patients and found male predominance. After proper analysis of the biopsy reports, we found 4 (0.8%) cases of IgA Glomerulopathy in the last 10 years. The male to female distribution was found to be 3:1 with the mean age of 22±2 years. At our setup, indications of the renal biopsy included nephrotic syndrome, nephritic syndrome, acute kidney injury (AKI), rapidly proliferative glomerulonephritis, persistent proteinuria, and isolated hematuria.

A study conducted by Chang et al.[13] in East Asia showed prevalence of IgA as 28.3% in 1818 cases within 20 years among the Korean population. However, Li et al.[14] from China collected one of the largest data about IgAN with total number of biopsies about 13519 cases showed IgA as 45.26%. Data from other parts of the world like Finland by Wirta et al.[15] showed IgAN 34.9%, Briganti et al.[16] from Australia showed 8.6% and Swaminathan et al.[17] from USA showed prevalence of IgAN as 22%. Furthermore, we have found male predominance in IgA Nephropathy, with over all 75% male patients, in accordance with other studies[16-20].

Furthermore, a study conducted by Imtiaz et al.[18] in Pakistan at the Kidney Center Post Graduate Training Institute, over a duration of 18 years from January 1996-December 2013 revealed IgA as 2.6% among all the 1521 cases. Similarly, another major study conducted in Pakistan by Mubarak et al.[19] reported the prevalence of IgA as 1.5% among the 1793 cases. In a regional study conducted in Kerala, India by Gopaliah et al.[10], IgA found 23.33% among 271 patients as the most common primary glomerular lesion. In addition, Bakhit et al.[21] from Saudi Arabia collected data of 16 years and detected IgAN as 36.4.0% in 74 cases.

However, a study from India by Jamil et al.[22] showed different results, and prevalence was found more common in female patients with M:F ratio of 1:2. Since, hematuria is found to be the most primary presentation around the world and many studies conducted in different regions of the world over the specific timeperiod[10,13,23,24]. However, current study showed different results from a Pakistani study [19] that revealed nephrotic syndrome as the primary presentation. Chaudhry and colleagues[25] conducted a study between 2008 to 2014 and obtained a data of 142 cases on IgA nephropathy, which showed proteinuria as the most common presentation among the Pakistani population. In contrary, we found relatively a fewer number of patients with IgA nephropathy. This could be because of the insidious nature of the disease or the subtle symptomatology, which causes delay in the presentation. The socio-demographic differences could also affect the prevalence of the disease. Most of the patients presented to Jinnah Postgraduate Hospital belonged to a low-middle socioeconomic class. However, a study from the Aga Khan Hospital reported a higher prevalence of the disease, which highlighted some socio-demographic factors that might be responsible for prolonged illness[12]. Therefore, we may suggest that further large-scale studies should be conducted to ascertain these assumptions in more detail.

CONCLUSION

Prevalence of IgA nephropathy is only 0.8% of the cases in the last 10 years. In addition, mostly male

predominance was presented among the patients with hematuria. Thus, IgA nephropathy has a wide variation in prevalence in different countries, regionally as well as globally.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Jinnah Postgraduate Medical Centre for facilitating the research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

This observational study was performed at department of Nephrology, JPMC Karachi. The approval for data retrieval was taken from Ethical Board of the above hospital before the start of study with reference no F.2-18/2019-GEN/37670-A/JPMC issued on 23/12/2019.

PATIENTS CONSENT

Informed consent from patient or family member was already taken before performing biopsy.

AUTHORS' CONTRIBUTION

MA, SA, AE, GU, NN, AMJ and HI had designed, directed, and coordinated the study, created study plan, analyzed the data, studied the renal biopsy reports and written the manuscript.

REFERENCES

1. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. Clin J Am Soc Nephrol. 2017;12(4):6776-86.
2. Berger J. IgA glomerular deposits in renal disease. Transplant Proc. 1969;1(4):939-944.
3. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, *et al.* Oxford classification of IgA nephropathy 2016: an update from the IgA nephropathy classification working group. Kidney Int. 2017;91(5):1014-1021.
4. AlYousef A, AlSahow A, AlHelal B, Alqallaf A, Abdallah E, Abdellatif M, *et al.* Glomerulonephritis histopathological pattern change. BMC Nephrol. 2020;21:1-7.
5. McGrogan A, Franssen CF, de VriesCS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011; 26(2):414-430.
6. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, *et al.* Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8(6):e1002765.
7. Okpechi IG, Ameh OI, Bello AK, Ronco P, Swanepoel CR, Kengne AP. Epidemiology of histologically proven glomerulonephritis in Africa: a systematic review and meta-analysis. PLoS One. 2016;11(3): e0152203.
8. Jennette JC, Wall SD, Wilkman AS. Low incidence of IgA nephropathy in blacks. Kidney Int. 1985; 28(6):944-950.
9. Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, *et al.* IgA nephropathy. Nat Rev Dis Primers. 2016;2(1):1-20.
10. Gopaliah L, Sudakaran I, Nalumakkal S, Narayanan R, Vareed B. Spectrum of biopsy-proven renal diseases: A single center experience. Saudi J Kidney Dis Transpl. 2018;29(2):392-400.
11. Floege J, Feehally J. IgA nephropathy: recent developments. J Am Soc Nephrol. 2000; 11(12): 2395-2403.
12. Muzaffar S, Azad NS, Kayani N, Pervaz S, Ahmed A, Hasan SH. The frequency of IgA nephropathy at a single center in Pakistan. J Pak Med Assoc. 2003;53(7):301-305.
13. Chang JH, Kim DK, Kim HW, Park SY, Yoo TH, Kim BS, *et al.* Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant. 2009;24(8):2406-2410.
14. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004;66(3):920-923.
15. Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. Nephrol Dial Transplant. 2008;23(1):193-200.
16. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, *et al.* The incidence of biopsy-proven glomerulonephritis in Australia. Nephrol Dial Transplant. 2001;16(7):1364-1367.
17. Swaminathan S, Leung N, Lager DJ, Melton LJ, Bergstralh EJ, Rohlinger A, *et al.* Changing incidence of glomerular disease in Olmsted County, Minnesota: A 30-year renal biopsy study. Clin J Am Soc Nephrol. 2006;1(3):483-487.
18. Imtiaz S, Drohlia M, Nasir K, Salman B, Ahmad A. Analysis of renal diseases detected in renal biopsies of adult patients: A single-center experience. Saudi J Kidney Dis Transpl. 2017;28(2):368-378.
19. Mubarak M, Kazi JI, Naqvi R, Ahmed E, Akhter F, Naqvi SA, *et al.* Pattern of renal diseases observed in native renal biopsies in adults in a single centre in Pakistan. Nephrol. 2011;16(1):87-92.
20. Bandi V, Nalamati A, Kasinaboina B, Chundru S. Epidemiologic data of biopsy-proven renal diseases: Experience from a single center in South India. Saudi J Kidney Dis Transpl. 2019;30(2):478-491
21. Bakhit AA, Alhamad YM, Al Oudah N, Al-mezaini LI, Ahmed N. Spectrum of biopsy-proven kidney diseases in older Saudi adults, 2001-2017. J Clin Exp Nephrol. 2018;3(3):15.
22. Jamil M, Bhattacharya P, Raphael V, Khonglah Y, Lyngdoh M. Spectrum of glomerular diseases in adults: a study from North Eastern India. J Assoc Physicians India. 2018;66:36-39
23. Ikram M, Muhammad S, Ali A, Muhammad N, Bahadur K, Haq MI. Frequency of histopathological patterns of renal diseases in a tertiary care hospital. J Postgrad Med Inst. 2017;31(2):15-19.
24. Al-Imam A, Ali MA, Al-Mukhtar SE. The spectrum of biopsy-proved kidney disease: A retrospective single center study in Erbil-Iraq. Asian J Med Sci. 2019;10(2):46-51.
25. Chaudhry Z. From the chief editor's desk. J Coll Physicians Surg Pak. 2019;29(1):1-1