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THE CLINICAL SPECTRUM OF IMMUNOGLOBULIN A NEPHROPATHY

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ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that occurs globally and is documented as a major cause of end-stage renal disease worldwide. IgAN is more common in males than in females. The prevalence of IgAN in Iraq is 3.5% from single center study in 2013. Patients with IgAN may be asymptomatic, with persistent microscopic hematuria and proteinuria and often hypertension. IgAN appears to be a systemic disease in which the kidneys are damaged as innocent by standers, because IgAN frequently recurs after transplantation. **Aim of the study:** To study the cases of IgAN with regard to their clinical, light microscopic, immunofluorescence presentation and compared our findings with the other published researches inside and outside Iraq. **Patients and Methods:** This is a retrospective study in lasted two years from January 2017 to December 2018. Patient's data were collected from 64 patients who suspected to have primary glomerulonephritis including IgAN. The patients were presented in the last two years in Alkafeel Hospital / Kerbala - Iraq and Al-Hussein Teaching Hospital, Al-Hussain Medical City, Kerbala Health Directorate / Kerbala - Iraq, referred to nephrology center at different duration times. All patients underwent routine physical and various investigations in the form of complete blood count, erythrocyte sedimentation rate, renal function test, electrolytes, liver function test, bleeding profile (PT, PTT, INR), bleeding time, virology screen, urinalysis, 24 hours urine protein and/or spot urine protein to creatinine ratio, and glomerular filtration rate. In addition to the above mentioned workup, specific investigations were done including: (ANA, Anti-ds DNA) by ELISA technique, (C3, C4) by nephelometry technique, and serum IgA level in some patients. All patients underwent kidney biopsy according to standard procedure by Kerstin Amann, and their tissue specimens were studied in the laboratory with LM by using the following stains: Hematoxylin and eosin, Periodic acid–Schiff (PAS), Trichrome, Methenamine silver. In addition, with IF microscope reagents, the relationship between the clinical presentations and IF deposits in kidney biopsy of all patients were studied using the statistical analysis of Pearson correlation and single table student's T test. A P value <0.05 was considered statistically significant. **Results:** The number of patients that confirmed to have IgAN were 14 patients, so the prevalence of IgAN from primary GN was 23 % female to male ratio was 1.3/1. Most of the patients presented with hematuria 93 % followed by hypertension 50% and proteinuria 43 %. The results showed that most common histopathological results is class 1 (50%), followed by class 2 (36%). The results of the severity of immune deposits showed that most IF deposits were +2 (moderate intensity) that represent 71% of cases and followed by +1 (mild intensity) that represent 29% of cases. There was no statistically significant correlation between the age of patients at presentation and renal outcome (according to HAAS classification). There was statistically significant correlation between each of hematuria at time of presentation and class 1 HAAS classification in the biopsy from patients with, renal impairment at time of presentation and class 2 HAAS classification in the biopsy of patients with IgAN, hematuria and the severity of IgA deposits by IF and renal impairment at presentation and the severity of IgA deposits by IF, renal impairment at presentation was more sensitive to +2 (moderate intensity deposits). There was no significant correlation between hypertension, edema, proteinuria and recent URTI at presentation with renal outcome (HAAS classification) and history of recent upper respiratory tract infection and the severity of IgA deposits by IF. **Conclusions:** Prevalence of IgAN is 23% from primary GN. Hematuria is the most common clinical presentation in IgAN. IF deposits are mainly granular pattern and almost mesangial in site in IgAN. Most common HAAS classification is class 1. Most IF deposits are moderate in intensity (+2). Males are more sensitive to class 1 HAAS classification than female. Patients with hematuria at presentation are more sensitive to class 1 HAAS classification. Renal impairment at presentation is more sensitive to class 2 HAAS classification. No correlations between proteinuria, edema, hypertension and history of recent upper respiratory tract infections with renal outcome (According to HAAS classification). Patients with hematuria at presentation are more sensitive to moderate intensity (+2) of IgA deposits by IF. Renal impairment at presentation is more sensitive to moderate intensity (+2) of IgA deposits by IF. No correlation between proteinuria, edema, hypertension and history of recent upper respiratory tract infection with the severity of IgA deposits by IF.

KEYWORD: IgAN, IF, GN, hematuria, HAAS, proteinuria.

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that occurs globally and is recognized as a major cause of end-stage renal disease (ESRD) worldwide.[1,2] IgA nephropathy was first described by Berger and Hinglais in 1968, and is also known as Berger disease.[3,4] Distribution of IgA nephropathy varies in different geographic regions throughout the world. IgA nephropathy is observed in up to 40% of all biopsies performed for glomerular disease in Asia, compared with 20% in Europe and 10% in North America. The prevalence of IgA nephropathy in Iraq is 3.5% from single center study in 2013.[5]

The prevalence of IgAN is highest in geographic areas with large numbers of endemic helminthic species that infest humans, and most of the IgAN susceptibility loci identified by genome-wide association studies include genes involved in the maintenance of the intestinal epithelial barrier and response to mucosal pathogens, which would confer protection against helminthic infestation. Thus, the increased risk of IgAN in these populations may be an untoward consequence of a protective adaptation to helminthic infections. It would also explain the association of mucosal infections as a frequent trigger for IgAN.[6] IgAN is more common in males than in females. Virtually all studies show a male predominance of at least two to one, with reported ratios of up to six to one.[7] IgAN can affect all ages but is more common in the 2nd and 3rd decades of life. The condition is uncommon in children younger than ten years. Although IgAN usually follows a benign course, end-stage renal disease (ESRD) develops in 15-20% of patients within ten years of onset and in about 25-30% of patients by twenty years. It tends to progress slowly, with progression to ESRD within 25 years in about half of the affected patients.[8] Efforts have been made to determine clinical and histological features associated with progression to ESRD.[9,10] The likelihood of dialysis or death was recently estimated with the use of three risk factors that are documented at biopsy: urinary protein excretion of more than one gram per day, hypertension (>140/90 mm Hg), and severe histologic lesions on the basis of glomerular, vascular, tubular, and interstitial features.[11]

Patients with IgAN may be asymptomatic, with persistent microscopic hematuria and proteinuria and often hypertension. This presentation occurs mostly in adults. Impairment of renal function can occur in such cases, and remission is uncommon.[12]

Symptomatic presentations in patients with IgAN include (Episodic gross hematuria, Nephrotic syndrome – More than 3500 mg of proteinuria with edema, hypoalbuminemia, hypertension, and hyperlipidemia, Chronic renal failure, Rapidly progressive glomerulonephritis –This is sometimes seen as a late presentation, these patients may progress to needing renal replacement therapy rapidly).[13]

Physical examination findings in patients with IgAN are usually unremarkable. A minority of patients present with hypertension. More commonly, however, hypertension manifests later in the course of the disease or when patients develop chronic kidney disease and end-stage renal disease (ESRD). Nephrotic syndrome could manifest as edema in lower extremities.[13]

No specific histologic features that can differentiate primary from the so-called secondary cases. Systemic disorders associated with secondary IgA nephropathy include gastrointestinal and liver disorders, viral infections, neoplasia and others such as chronic mucosal infections (streptococcus, staphylococcus), chronic infections (staphylococcus), malaria, schistosomiasis and psoriasis.[14]

In the present study, the aim is to study the cases of Ig-AN who presented in the last two years with regard to their clinical, light microscopic (LM), immunofluorescence (IF) presentation and compared our findings with the already published researches inside and outside Iraq.

PATIENTS AND METHODS

This is a retrospective study lasted two years from January 2017 to December 2018. Patient's data were collected from 64 patients who suspected to have primary glomerulonephritis including IgAN. The patients were referred to nephrology center in (Al-Hussein Teaching Hospital, Al-Hussein Medical City, Kerbala Health Directorate/Kerbala - Iraq and AL-Kafeel subspecialty hospital in Karbala at different duration time.

The presentations in patients with suspected IgAN include the following (inclusion criteria): Episodic gross hematuria, Nephrotic syndrome: More than 3500 mg of proteinuria with edema, hypertension, hyperlipidemia, and hypoalbuminemia, Chronic renal failure, Rapidly progressive GN: This is seen as a late presentation, these patients may progress to needing renal replacement therapy rapidly.[13] For all patients detailed history and physical examination were done.

All patients underwent routine investigations in the form of complete blood count, erythrocyte sedimentation rate, renal function test, electrolytes, liver function test, bleeding profile (PT, PTT, INR), bleeding time, virology screen, urinalysis, 24 hours urine protein and/or spot urine protein to creatinine ratio, and glomerular filtration rate.[15] In addition to the above mentioned workup, specific investigations were done for all patients including: (ANA, Anti-ds DNA) were done by ELISA technique, (C3, C4) by nephelometry technique, and serum IgA level in some patients.

The prevalence of IgAN from primary GN, age of distribution of the disease, male to female ratio, most common clinical presentation and its relation to the sex,

most common IF finding and its relation to clinical findings were studied.

All patients were informed about the indications, method used and possible complications of kidney biopsy procedure beforehand, and assigned informed consents were taken. The procedure was done according to the standard guideline by Kerstin Amann.[5]

We took three to four cores from either the left or right kidney under ultrasound guidance, with assistance of trained interventional radiologist.

One to two cores were kept in 5% formalin contained test tube, two cores were kept in 0.9% isotonic saline contained tube, and all the specimens were sent immediately after the procedure to the laboratory for Immunofluorescence and light microscopic study.[5]

Each specimen was studied by two different pathologist and specimen should contain more than or equal to ten glomeruli for LM study, and more than five glomeruli for IF study.[5] For IF study, a semi quantitative scale was used.

Four patients were excluded from the study due to the following reasons: two of them did not complete the investigations required for the study, two patients the biopsy not contained proper amount of glomeruli that needed for the study.

Statistical package for social sciences (SPSS) version 24 computer program by choosing chi square test, Pearson correlation, and single table "T" test. P values <0.05 was considered statistically significant.

RESULTS

The study included 64 patients that suspected to have primary GN, four patients were excluded from the study due to the following reasons: two of them did not complete the investigations required for the study, two patients the biopsy not contained proper amount of glomeruli that needed for the study.

The number of patients that confirmed to have IgAN were 14 patients, so the prevalence of IgAN from primary GN in this study was **23%**. From those 14 patients, eight were females and six were males. The age at presentation of patients with IgAN described in **Table 1**.

Table 1: Shows the age at presentation of patients with IgAN.

	Age, year					
	11-20	21-30	31-40	41-50	51-60	Total
Patients	4	2	4	3	1	14
Percentage (%)	28.6	14.3	28.6	21.4	7.1	100

Most of the patients in this study presented with Hematuria 93% followed by Hypertension 50% and Proteinuria 43%, see **Table 2**.

Table 2: Shows the Percentage of clinical presentations of patients with IgAN.

Clinical presentation	Percentage
Hematuria	93%
Hypertension	50%
Proteinuria	43%
Renal impairment	14%
Edema	21%
Anemia	7%
Recent upper respiratory tract infection	14 %

According to HAAS classification of IgAN, the results of this study showed that most common histopathological results is class 1 (50%), followed by class 2 (36%), see **Table 3**.

Table 3: Histopathological spectrum of renal biopsy results according to HAAS classification.

HAAS classification	Number of Patients (%)
Class 1	7 (50%)
Class 2	5 (36%)
Class 3	2 (14%)
Class 4	0
Class 5	0

The granular pattern of IF deposits were present in all IgAN patients, and all these IF deposits presented in the mesangium. The results of the severity of immune deposits in this study showed that most IF deposits were +2 (moderate intensity) that represent 71% of cases and followed by +1 (mild intensity) that represent 29% of cases. All biopsies stained negative for C1q and C3, IgA found in all biopsies (100%) and IgG stained positive in 50% of cases and IgM stained positive in 21% of cases. Regarding the correlations between age at presentation and the renal outcome (According to HAAS classification) in patients with IgAN in this study, there was no statistically significant correlation (Chi square = 14.15, p value = 0.078), see **Table 4**.

Table 4: Correlation between age at presentation and renal outcome (HAAS classification).

Age * HAAS classification Cross tabulation							
		HAAS classification					Total
		class 1	class 2	class 3	class 4	class 5	
Age	11-20 years	4	0	0	0	0	4
	21-30 years	1	0	1	0	0	2
	31-40 years	2	1	1	0	0	4
	41-50 years	0	3	0	0	0	3
	51-60 years	0	1	0	0	0	1
Total		7	5	2	0	0	14
		Chi square = 14.15			p value= 0.078		

Regarding the correlations between gender and the renal outcome (According to HAAS classification) in patients with IgAN in this study, there was statistically significant correlation (Chi-square = 6.125, p value= 0.047), we found that males have more sensitive to class 1 than females, see **Table 5**.

Table 5: Correlation between gender and renal outcome (HAAS classification).

Gender * HAAS classification Cross tabulation							
		HAAS classification					Total
		class 1	class 2	class 3	class 4	class 5	
Gender	Male	5	0	1	0	0	6
	Female	2	5	1	0	0	8
Total		7	5	2	0	0	14
		Chi-square = 6.125			p value= 0.047		

The statistical correlation between Hematuria, Proteinuria, Edema, Hypertension, Renal impairment and history of recent upper respiratory tract infection (URTI) with renal outcome of IgAN patients (According to HAAS classification) described in **Table 6**.

Table 6: Correlation between clinical presentations and renal outcome (HAAS classification).

Clinical presentation	HAAS classification					P value
	Class 1	Class 2	Class 3	Class 4	Class 5	
Hematuria : - Present	6	5	2	0	0	**0.037**
- Absent	1	0	0			
Proteinuria : - Present	2	3	1	0	0	0.059
- Absent	5	2	1			
Hypertension : - Present	2	4	1	0	0	0.14
- Absent	5	1	1			
Edema : - Present	2	2	1	0	0	0.13
- Absent	5	3	1			
Renal impairment : - Present	0	2	1	0	0	**0.046**
- Absent	7	3	1			
Recent URTI : - Present	2	0	0	0	0	0.061
- Absent	5	5	2			

There was statistically significant correlation between hematuria at time of presentation and class 1 HAAS classification in the biopsy from patients with IgAN (P value = 0.037) and between renal impairment at time of presentation and class 2 HAAS classification in the biopsy of patients with IgAN (P value = 0.046), while there was no significant correlation between hypertension, edema, proteinuria and recent URTI at

presentation with renal outcome (HAAS classification). The statistical correlation between hematuria, proteinuria, edema, hypertension, renal impairment and history of recent upper respiratory tract infection (URTI)
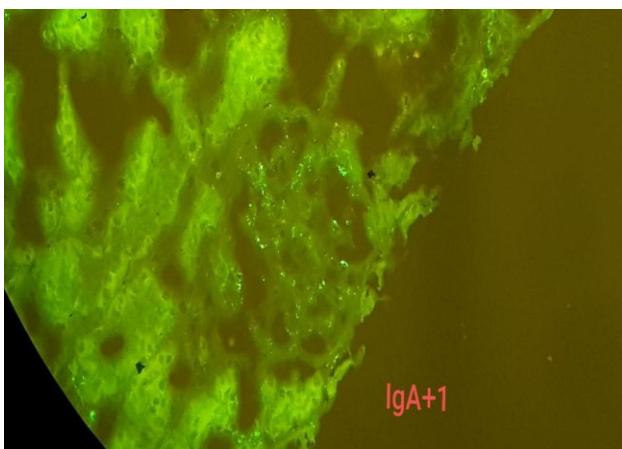
with the severity of IgA deposits in kidney tissue that seen by IF in the biopsy of patients with IgAN described in **Table 7**.

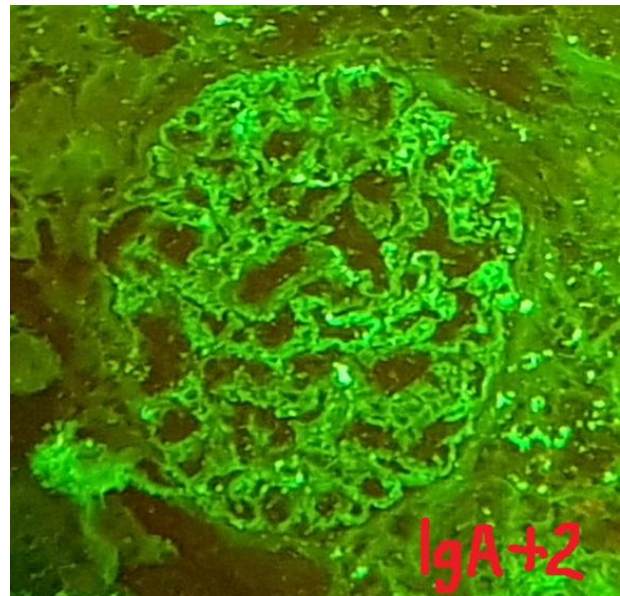**Table 7: Correlation between clinical presentations and the severity of IgA deposits in kidney tissue.**

Clinical presentation	Severity of IgA Deposits in IF				P value
	0	+1	+2	+3	
Hematuria : - Present	0	4	9	0	**0.031**
- Absent	0	0	1	0	
Proteinuria : - Present	0	2	4	0	0.066
- Absent	0	2	6	0	
Hypertension: - Present	0	2	5	0	0.94
- Absent	0	2	5	0	
Edema : - Present	0	1	4	0	0.071
- Absent	0	3	6	0	
Renal impairment : - Present	0	1	2	0	**0.033**
- Absent	0	3	8	0	
Recent URTI: - Present	0	1	1	0	0.061
- Absent	0	3	9	0	

There was statistically significant correlation between hematuria and the severity of IgA deposits by IF (P value = 0.031), the presence of hematuria at presentation was more sensitive to +2 (moderate intensity deposits), and between renal impairment at presentation and the severity of IgA deposits by IF (P value=0.033), renal impairment at presentation was more sensitive to +2 (moderate intensity deposits).

There was no statistically significant correlation between edema, hypertension, proteinuria and history of recent upper respiratory tract infection and the severity of IgA deposits by IF.


Figure 2: Shows IF study of 44-year-old female patient presented with hematuria, proteinuria, and hypertension, it shows +2 mesangial IgA deposits.

Fig. 1: Shows IF study of 34-year-old female patient presented with hematuria and she had history of chronic kidney disease in her family, it shows +1 mesangial IgA deposits.
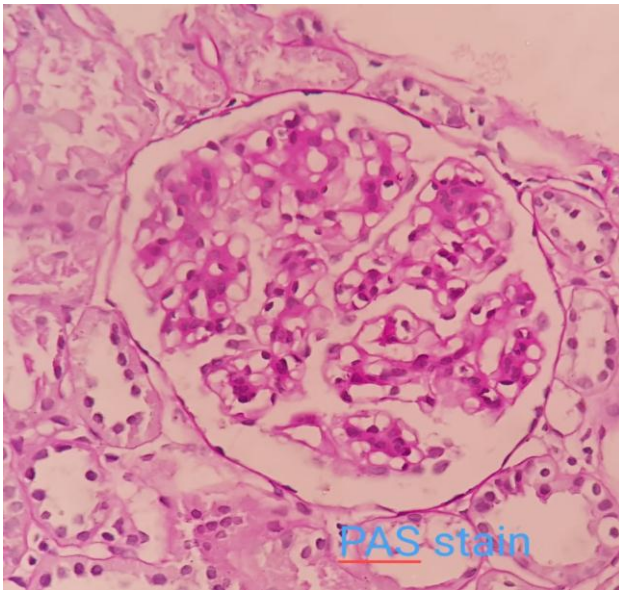
Figure 3: Shows LM study of 21-year-old male patient presented with hematuria for months prior to kidney biopsy, it shows segmental mesangial area expansion by PAS stain.
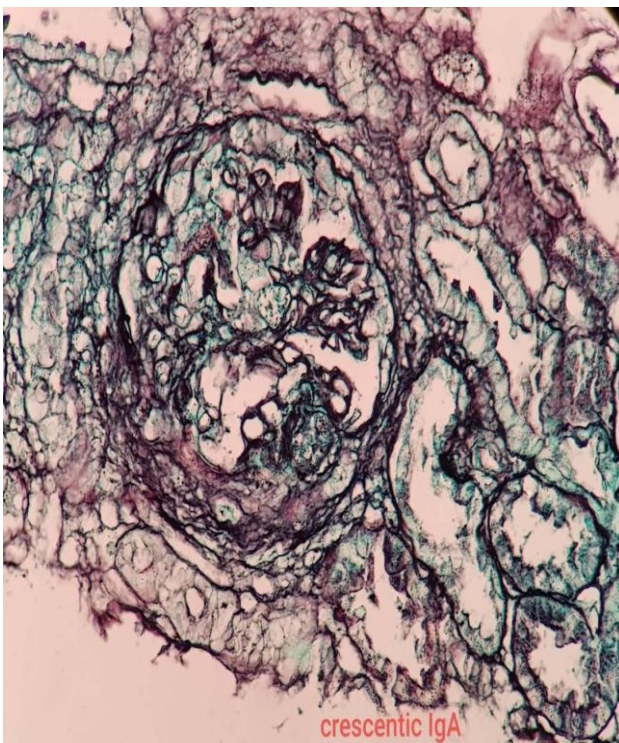
Fig. 4: Shows LM study of 43-year-old female presented with hematuria and renal impairment, it shows single glomerulus with large cellular crescent formation (extra capillary lesions), with marked collapse of capillary lumens in this glomerulus by silver stain:

DISCUSSION

Many renal studies of glomerulonephritis associated with mesangial IgA deposits and with other recent renal biomarkers have been published since the original report on IgAN by Berger and Hinglais. IgAN is observed in up to 40% of all biopsies performed for glomerular disease in Asia, compared with 20% in Europe and 10% in North America. High prevalence rates are observed in Singapore, Japan, Australia, Hong Kong, Finland, and southern Europe, whereas low prevalence rates are the rule in the United Kingdom, Canada, and the United States.[4,17] The prevalence of IgAN in Iraq is 3.5% from single center study in 2013.[5]

In current study, we reported that the prevalence of IgAN was 23% from primary GN, this high prevalence could be reflected to exclusion of secondary glomerular diseases in our study, and as the awareness and opportunity of medical facilities increase, the frequency of such diseases usually rises. The higher reported incidence of this disease in certain countries compared to others may reflect the practice of routine annual urinalysis in the countries with high incidence rates. IgAN is more common in males than in females. Virtually all studies show a male predominance of at least two to one, with reported ratios of up to six to one.[7]

The data observed that IgAN occurred in female more than in male (female to male ratio was 1.3/1), this is could be reflected to women constitute the highest percentage of the Iraqi population due to recurrent wars that had changed the demography and making the women dominant in all the aspects of life. Or this high ratio could be due to bias in selection of patients. IgAN can affect all age groups but is more common in the 2nd and 3rd decades of life. Eighty percent of patients are aged 16-35 years at the time of diagnosis. The condition is uncommon in children younger than ten years.[16]

The current study reported that IgAN occurred frequently in patients aged 11 to 20 years and 31 to 40 years; this could be reflected to that the mother's did not noticed hematuria in her child below 10 years, or misdiagnosed as infection or stone in many circumstances.

Most common histopathological results obtained of renal biopsy according to HAAS classification were class one (50%), class two (36%) followed by class three (14%), this may be related to the early recognition of symptoms by the patients and early diagnoses by renal biopsy and treatment before it became advanced. Other studies showed that most cases of IgAN were clustered in class three and class four.[18]

The most common clinical presentation of IgAN patients obtained were hematuria (93%), hypertension (50%), proteinuria (43%), edema (21%), renal impairment (14%), anemia (7%) and history of recent upper respiratory tract infections occurred in (14%) of patients. This difference in presentation can be attributed to the difference in the nature of the disease, which could be linked to genetic factors.

Patients with IgAN may be asymptomatic, with persistent microscopic hematuria and proteinuria and often hypertension. Approximately 40-50% of patients present with one or recurrent episodes of gross (visible) hematuria, often accompanying an upper respiratory tract infection.[12] Another 30-40% have microscopic hematuria and usually mild proteinuria and are incidentally detected on a routine examination or during a diagnostic evaluation for chronic kidney disease. Less than 10% present with either nephrotic syndrome or an acute rapidly progressive GN characterized by hypertension, edema and renal insufficiency as well as hematuria.[12,19]

In this study, we use HAAS classification to classify the disease and to assess the renal outcome because it was simple to interpret data according to it and all histopathological reports depend on it and the data obtained that there was no statistically significant correlation between the age of patients at presentation and renal outcome (According to HAAS classification).

Granular IF deposits in all patients were obtained. This indicates that IF deposits are mainly granular pattern in IgAN patients. To date, only a few studies have evaluated differences in clinicopathologic features and the prognosis of IgAN between the different genders, in this study, we reported that there was statistically significant correlation between gender of patients and renal outcome according to HAAS classification, we found that male patients were more sensitive to class 1 HAAS classification than female, the results of the study are different from previous studies that showing that females had milder pathologic changes whereas males were shown to have more aggressive forms.[20] The small sample in current study may be one reason, beside early suspicion and diagnosis with kidney biopsy.

They found that male IgAN patients presented with worse clinicopathological features than female patients. However, no significant difference was observed in long-term renal survival between male and female patients after frequency matching of baseline eGFR level. In addition, they found that male and female patients shared similar risk factors, including low eGFR, heavy proteinuria and extensive segmental sclerosis, but the proportion of global glomerulosclerosis was a significant risk factor only in male patients. In a study by Goto M, male gender, rather than female gender, was associated with the risk of ESRD.[21] In addition, according to correlation analysis of the main prognostic risk factors affecting the progression of IgAN, Riispere Ž et al. concluded that IgAN progressed more rapidly in males compared with females.[22] The possible mechanisms underlying the renal protective role of female gender seem to be related to oestrogen.[23]

In this study, we reported that there was statistically significant correlation between hematuria at presentation and class 1 HAAS classification, patients presented with hematuria were more sensitive to class 1, and this was different from other studies, that showed the hematuria was associated with aggressive histologic findings and correlated with a poor prognosis. This confirmed by the Southwest Pediatric Nephrology Study Group.[20] Moreover, Bennet and Kinciad-Smith reported that renal function became significantly worse in those with macroscopic hematuria, and emphasized the high incidence of crescent formation in these cases.[24] However, Clarkson et al demonstrated that renal function and lesions were significantly better in patients with macroscopic hematuria than in those without it.[25]

There was statistically significant correlation between renal impairment at time of presentation and class 2 HAAS classification, and this could be reflected to underdiagnosis of IgAN as a cause of renal impairment in our country and the limitations to do kidney biopsy, and this was different from other studies that showed that renal impairment at time of presentation was associated with class 4 and 5 HAAS classification than class 1.[26]

We reported that there was no statistically significant correlation between hypertension, edema, proteinuria and history of recent upper respiratory tract infection with renal outcome (According to HAAS classification). Bartosik *et al* proved that the clinical parameters, such as hypertension and severity of proteinuria, appear to be stronger prognostic indicators than histological findings.[27] Moreover, Van Der Peer *et al* found that those with higher levels of hypertension and proteinuria and more marked histologic findings had greater deterioration of their renal functions during follow–up when compared with those with lower levels and less marked findings.[28] Alsaegh found that arterial hypertension presence at time of biopsy is a negative clinical prognostic marker, even before the occurrence of ESKD.[29]

A statistically significant correlation between hematuria and severity of IgA deposits by IF was obtained, the presence of hematuria occurred more with +2 (moderate intensity deposits), also a statistically significant correlation between renal impairment at presentation and the severity of IgA deposits by IF, renal impairment at presentation was more sensitive to +2 (moderate intensity deposits). Further studies recommended determining the exact correlation between clinical presentation and the severity of IgA deposits. Whereas, there was no statistically significant correlation between edema, hypertension, proteinuria and history of recent upper respiratory tract infection and the severity of IgA deposits by IF, therefor we recommend further studies taking a big sample to study this correlation.

CONCLUSION

We can conclude that:
- Prevalence of IgAN is 23% from primary GN.
- Hematuria is the most common clinical presentation in IgAN.

- IF deposits are mainly granular pattern and almost mesangial in site in IgAN.
- Most common HAAS classification is class 1.
- Most IF deposits are moderate in intensity (+2).
- No statistically significant correlation between age at presentation and renal outcome (According to HAAS classification).
- Males are more sensitive to class 1 HAAS classification than female.
- Patients with hematuria at presentation are more sensitive to class 1 HAAS classification.
- Renal impairment at presentation is more sensitive to class 2 HAAS classification.
- No correlations between proteinuria, edema, hypertension and history of recent upper respiratory tract infections with renal outcome (According to HAAS classification).
- Patients with hematuria at presentation are more sensitive to moderate intensity (+2) of IgA deposits by IF.
- Renal impairment at presentation is more sensitive to moderate intensity (+2) of IgA deposits by IF.
- No correlation between proteinuria, edema, hypertension and history of recent upper respiratory tract infection with the severity of IgA deposits by IF.

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