Clinicopathological Findings of IgA Nephropathy in Children and Adolescents; (Multicentn Study)

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ABSTRACT:

BACKGROUND:

IgA nephropathy (IgAN) is the most common lesion found to cause primary glomerulonephritis throughout most developed countries of the world. Patients may present at any age, but there is a peak incidence in the second and third decades of life.

OBJECTIVE:

To study the demographic, clinical and laboratory findings of IgAN patients including children and adolescents.

METHODS:

The medical records of 30 patients with IgAN were retrospectively reviewed and assessed. Patients enrolled in this study were between 1-18 years old diagnosed as IgAN in the period from January 2010 to the end of December 2012 being treated and followed in the main three centers of treating cases of pediatric nephrology in Baghdad (Al-karama teaching hospital, Central Child Teaching Hospital and Baghdad Medical City) that receive referral cases from all Iraqi governorates.

RESULTS:

The total number of cases enrolled in this study was 30 patients, with males being 19 and females being 11. The male to female ratio was 1.72:1. Family history of chronic renal disease was found in 10 patients (33%). History of pharyngitis was found in 16 patients (53.3%). Macroscopic hematuria was found in 24 patients (80%), followed by edema in 18 patients (60%), and followed by hypertension in 15 patients (50%). The most common laboratory findings among study group was microscopic hematuria (29 patients, 96.7%), followed by proteinuria in 22 patients (73.3%). Renal biopsy was done for all patients for the diagnosis of IgAN. The distribution of histopathology staging system was: Stage (1) 14 patients, Stage (2) 8 patients, Stage (3) 5 patients, Stage (4) 2 patients and Stage (5) 1 patient (46.7%, 26.7%, 16.7%, 6.7% and 3.3% respectively). The study showed that 24 patients were found to have IgA deposited solely (80%). Out of the total 12 patients presented with hematuria, nine of them (75%) showed stage 1 disease on histopathology study. Two patients were noticed to have other associated autoimmune diseases, one with hepatitis and another with ulcerative colitis.

CONCLUSION:

Further studies in large number of patients are needed in order to confirm the findings in this study and to establish the best therapeutic choice for IgAN. The need for immunofluorescence examination of the renal biopsies in suspected cases is recommended.

KEY WORDS: IgAN, nephritis, nephrotic, hematuria.

INTRODUCTION:

IgA nephropathy (IgAN) is the most common lesion found to cause primary glomerulonephritis throughout most developed countries of the world (1). Patients may present at any age, but there is a peak incidence in the second and third decades of life. IgAN occurs with greatest frequency in Asians. The reported incidence of mesangial IgA deposition in apparently healthy individuals ranges between (3%-16%) (2). Many patients with IgAN are detected on routine urine screening. Patients with IgAN typically present in one of three ways: Approximately (40%-50%) present with one or

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recurrent episodes of visible hematuria, usually following an upper respiratory infection or urinary tract infection. Another (30%-40%) have microscopic hematuria and usually mild proteinuria, and are incidentally detected on a routine examination. Less than 10% present with either nephrotic syndrome or acute rapidly progressive glomerulonephritis picture [3] The suspicion of a diagnosis of IgAN is generally based upon the clinical history and laboratory data. The diagnosis can be confirmed only by kidney biopsy with immunofluorescence studies for IgA deposits [4]. Patients with IgAN who have little or no proteinuria (less than 500 to 1000 mg/day) have a low risk of progression, at least in the short term. However, proteinuria and renal insufficiency develop in a substantial proportion of patients over the long term [5]. The optimal approach to the treatment of IgAN is uncertain. (6)

AIMS OF STUDY:

To study the demographic, clinical and laboratory findings of IgAN patients including children and adolescents.

PATIENTS AND METHODS:

The medical records of 30 patients with IgAN were retrospectively reviewed and assessed. Patients between 1-18 years old diagnosed as primary IgAN in the period from January 1st, 2010 to December 31st, 2012 being treated and followed in three centers of pediatric nephrology in Baghdad (Al-karama Teaching Hospital, Central Child Teaching Hospital and Baghdad Teaching Hospital) that receive referral cases from all hospitals in the Iraqi governorates. The diagnosis was made on immunostaining of renal biopsy showing mesangial deposits of IgA as predominant or co-dominant immunoglobulin. The assessment of histopathology was depending on Hass classification (Five stages were mentioned by Hass classification system including the followings: Stage 1: minimal or no mesangial hyper cellularity without glomerular sclerosis, Stage 2: focal and segmental glomerular sclerosis without active cellular proliferation, Stage 3: focal proliferative glomerulonephritis, Stage 4: diffuse proliferative glomerulonephritis, and Stage 5: any biopsy showing more than or equal to 40% globally sclerotic glomeruli and/or more than or equal to 40% estimated cortical tubular atrophy or loss) (7). Blood and urinary laboratory tests were performed including serum creatinine, blood urea, and urinalysis including urine for proteins. The review chart includes name, age, gender, family history of renal diseases, and history of pharyngitis, associated diseases as arthritis and hepatitis, thorough physical examination, and investigations for proteinuria, microscopic hematuria, and renal function results. The clinical presentation at time of diagnosis was assessed. The results of renal biopsy were recorded including the histological grading of renal biopsy. The timing of renal biopsy was decided according to the indication in each patient. There were no specific clinical criteria for entry apart from the exclusion previously mentioned. As such, the patients' population that was selected for the study reflects the variety of opinion among pediatric nephrologists regarding the necessity for renal biopsy in children presenting with idiopathic hematuria with or without proteinuria. The period of observation of patients from clinical detection of renal disease varies from six months to three years. Patient data were tabulated and processed using SPSS (Statistical package for the social sciences) for windows. P-values equal or less than 0.05 were considered significant (8).

RESULTS:

The total number of cases enrolled in this retrospective study was (30), with males being 19 and females being 11. The male to female ratio was 1.72:1. The age range in this study was 2 to 18 years with a median of 10 years. Two patients were having other associated immune diseases (one with hepatitis C and one with ulcerative colitis). Family history of chronic renal disease was found in 10 patients (33.3%). History of pharyngitis was found in 16 patients (53.3%). (Table.1)

Table.(2) showed the clinical and laboratory features at time of presentation among patients with IgAN. Macroscopic hematuria was found in 24 patients (80%), followed by edema in 18 patients (60%), and hypertension in 15 patients (50%). The most common laboratory findings among study group was microscopic hematuria in 29 patients (96.7%), followed by proteinuria in 22 patients (73.3%) and impaired renal function in 10 patients (33.3%).

Regarding type of proteinuria, seventeen patients were noticed to have a proteinuria of nephrotic range (56%), while 5 patients (16.7%) were having proteinuria of nephritic type. Proteinuria was not detected in 8 patients (26.7%). (Table.3)

The presentation of patients with IgAN was classified into four categories according to the primary clinical diagnosis; Isolated Hematuria, Nephritis, Nephrotic, and Rapidly Progressive Glomerulonephritis. Twelve patients presented with hematuria and another (12) with Nephritis. Those were followed by Nephrotic syndrome in 5 patients, and Rapidly Progressive

Glomerulonephritis in 1 patient (40%, 40%, 16.6%, and 3.3% respectively). The five patients with nephrotic syndrome presentation were steroid resistant (3/5 patients; 60%) and steroid sensitive but with frequent relapses (2/5 patients; 40%). (Table.4)

Renal biopsy was done for all of the 30 patients for the diagnosis of IgAN. The distribution of histopathology staging system (Hass classification) was found with the following frequency: Stage (I) 14 patients, Stage (II) 8 patients, Stage (III) 5 patients, Stage (IV) 2 patients and Stage (V) 1 patient (46.7%, 26.7%, 16.7%, 6.7% and 3.3% respectively). (Table.5)

Table. (6) Shows the immunostaining features of renal biopsy specimens of the study group. It showed that 24 patients were found to have IgA deposited solely (80%). IgA and C3 deposition was found in the biopsies of 4 patients (13.3%).

Table. (7) Shows the frequency of deposition of IgA among renal biopsy specimens. It shows 9 patients with strong deposition of IgA in their renal specimens (30%) and labeled as (+3), moderate deposition (+2) of IgA was found in 20 (66.6%), while one patient with weak deposits of IgA (+1).

Table 1: Demographic and lab finding of 30 patients with IgAN.

Item	No (%)
Gender	Male --- 19 (63.3)
	Female ---11 (36.7)
Associated diseases	Negative --- 28 (93.3)
	Positive --- 2 (6.7)
History of pharyngitis	16(53.3)
Family history of renal disease	10(33.3)

Table 2: Clinical presentation at time of diagnosis among patients with IgAN.

Item	No (%)
Clinical	
Macroscopic hematuria	24 (80)
Edema	18 (60)
Hypertension	15 (50)
Laboratory	
Microscopical hematuria	29 (96.7)
Proteinuria	22 (73.3)
Impaired renal function	10 (33.3)

Table 3: Range of proteinuria among patients with IgAN.

Item	No (%)
Nephrotic	17 (56.7)
Negative	8 (26.7)
Nephritic	5 (16.7)
Total	30 (100)

Table 4: Classification of first time presentation of patients with IgAN.

Item	No (%)
Isolated Hematuria	12 (40)
Nephritis	12 (40)
Nephrotic syndrome	5 (16.6)
RPGN*	1 (3.3)

* Rapidly progressive glomerulonephritis

Table 5: Renal biopsy histopathology staging system among 30 patients with IgAN (Hass classification).

Staging*	No (%)
Stage I	14 (46.7)
Stage II	8 (26.7)
Stage III	5 (16.7)
Stage IV	2 (6.7)
Stage V	1 (3.3)

Table 6: Immunostaining findings in renal biopsy specimens of IgAN patients.

Immunostaining	No.	%
IgA	24	80
IgA+C3	4	13.3
IgA+IgG	1	3.3
IgA+IgG+IgM	1	3.3

Table 7: Frequency of IgA deposition in renal biopsy specimens in study group.

Degree	No.	%
+3 - Strong	9	30
+2 - Moderate	20	66.6
+1 - Weak	1	3.3

DISCUSSION:

IgAN is the most common lesion found to cause primary glomerulonephritis throughout most developed countries of the world [1]. The male: female ration in this study was 1.7:1, with male preponderance as in other international literatures and textbooks [9]. In Khawajah sudy from Saudi Arabia in 2010(10), the ratio was 2.8:1 and this difference may be difference between Iraq and Saudi Arabia may related to cultural issues where females tends to avoid such investigations but in this context, even in other countries, it has to be remembered that usually more male undergo renal biopsy than female. In one study the research showed the male to female ratio was 58:22 (11). Adding to that, these studies in comparison used to take both adults and pediatric ages enrolled in studies. Two of the study group patients, were noted to have associated diseases; one with hepatitis C virus infection, the other was associated with Ulcerative colitis. In other study, Filiopoulus study(12) in 2010 from Greece showed a case report association between IgAN and inflammatory bowel disease. A pathophysiological link between inflammatory bowel disease and IgAN might offer an additional agreement for such a local immunosuppressive effect. Immune complex glomerulonephritis particularly IgAN is a rarely described extra intestinal manifestation of inflammatory bowel disease, that occurs in the setting of active bowel inflammation. Although there is increasing literatures reporting association between IgAN and inflammatory bowel diseases, whether these reports represent chance association of pathophysiological related conditions still remains a matter of debate (13). History of pharyngitis was reported in 53.3% of cases in current study, which was significantly higher than that mentioned in Saudi Arabia study which reported 9.6% (10). Family history of renal disease was shown in 33.3% of cases which suggest a role for genetic factors and assumes the future need for genetic analysis patients with positive family history of IgAN. A study from USA and Italy showed a close association with the trait 6q 22-23 in 60% of cases of familial IgAN (14). In this study, hematuria followed by proteinuria was the most common presentation findings which was similar to other studies like Khawajah et al study from Saudi Arabia in 2010 (10), Date et al study from India in 1987 (15)and Kitajima study from Japan 1983 (16). Impaired renal function was observed in 33.3% of patients, it was higher than Khawajah et al study showing 26.1% of his patients with impaired renal function and this difference may be due to the targeted study sample [pediatric and adolescence in this study versus pediatric, adolescent and adult group in Khawajah et al study] and may be due to late presentation of our cases (10). Nephrotic proteinuria was found in 56.7%, which was slightly higher than Khawajah et al from Saudi (10) and Barger J study from France (17) which showed nephrotic proteinuria in 40.5% and

48% respectively. Hematuria as a complaint was observed in 40% of patients, which was similar to other literatures as Yagucky Y et al (18) and Koyama et al (19) from japan. In current study, the histopathological staging score in renal biopsy showed that stage one [minimal or no mesangialhyper cellularity] was the most common class of IgAN [46.7%], followed by class two [focal and segmental glomerulosclerosis without cellular proliferation] in [26.7%]. In Khawajah study from Saudi (10), class two was the most common class [45.2%], which may be due to the target population study [pediatric and adolescents versus pediatric, adolescent and adults]. However, reports from different parts of the world indicate difference in the pattern of disease class (13). This might be due to genetic or biological difference between populations in study. In recent review, Tumlin et al from USA in 2007 reported that proliferative and crescenting form (class four) was responsible for up to 30% of reported IgAN (20). Since the features of IgAN identified by light microscopy are nonspecific, immunofluorescence studies demonstrating a predominant deposition of IgA are essential to establish a definitive diagnosis of IgAN. The immune complexes are found predominantly within mesangial regions of glomeruli with focal paramesangial or sub-endothelial extension. In this study, IgA was found to be the dominant immunoglobulin in 30% of patients which was lower than Saudi Arabia study [60%]; it may be related to differences in the opinion of the pathologist deciding the frequency of deposition (10). A variety of other immunoglobulins and complements are frequently co-distributed with IgA, as reported by the literatures (9). Clinically in the early stages of the disease, many patients have no obvious symptoms and are unaware of any problems. In these patients, IgAN may be suspected only during routine screening of another condition. In the current study, only one such case was reported as she was investigating for ulcerative colitis and discovered to have microscopic hematuria. Most of our patients presented in later stages of the disease. Of note, no previous study conducted in Iraq about IgA nephropathy to be compared with the current study.

CONCLUSION:

Screening for IgAN by urine examination for early detection of the disease is important at school age group. Public health awareness is needed for early diagnosis. Further studies in larger number of patients are needed in order to confirm the findings of this study and to subsequently establish the best therapeutic choice for IgAN. Besides, the need of immunofluorescence examination of the renal biopsies in suspected cases to establish the diagnosis of IgAN is well recommended.

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