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Original Article

Retrospective analysis of clinical and pathological features of adult IgA nephropathy

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Abstract: We aimed to retrospectively analyze the clinical and pathological feature of 288 adult patients with primary IgA nephropathy (IgAN) diagnosed by renal pathology in Fujian Medical University Union Hospital, China. 288 adult IgAN patients were divided into two groups: group A, symptomatic IgAN group (146 cases) and group B, asymptomatic IgAN group (142 cases) identified by physical examination. Differences in clinical features and renal pathology classification were analyzed and compared. The body weight, BMI, serum IgA, IgG, IgA/C3, serum albumin and blood Hb in group A were significantly lower than those of group B ($P < 0.05$). Among 288 IgAN patients, the renal pathology classification mainly consisted of Lee SMK III, followed by IV, I, II, V. The differences in the renal pathology classification and Katafuchi R rating were not significant in the two groups. Additionally, renal antibody and complement deposits were mainly IgA+IgM+IgG+C3, and IgA deposit showed no obvious difference between the two groups. Renal biopsy should be performed properly for mild or even asymptomatic IgAN patients. Blood Hb serum albumin should be taken as important indicators during the follow-up time of IgAN patients, and the decline of these indicators may reveal the disease progression and the poor prognosis despite that they may be still in normal range at early stage.

Keywords: IgA nephropathy, retrospective analysis, clinical features, pathology classification

Introduction

IgA nephropathy (IgAN) is a primary glomerulonephritis which is commonly seen in Asia and even the world, shows diversity in both clinical and pathological indices, and presents differences between prognoses [1]. It can manifest from continuous asymptomatic microscopic hematuria to rapid progressive renal failure and histological patterns may range from minimal lesions to diffuse proliferative and crescentic glomerulonephritis [2-4]. IgAN accounts for about 30~40% of the primary glomerulonephritis in China, and about 15% IgAN patients will progress to end stage renal disease (ESRD) within 10 years [5]. In our clinical work we found that renal pathology might be very serious in some IgAN patients with mild clinical manifestations or even asymptomatic, and the study by Floege [6] indicated the heterogeneity of the course and prognosis of IgAN. For example, even if an IgAN patient's initial clinical or histological findings are comparatively mild, it may make progress to ERSD quickly [6]. In addition, Tan, et al. [7] also found that some patients with benign clinical features of IgAN also have severe renal histological damage. However, to date there are limited reports concerning the clinicopathological characteristics of IgAN diagnosed by physical examination worldwide. Therefore, we reviewed the clinicopathological characteristics of IgAN patients found by physical examination in our hospital, compared them with symptomatic IgAN patients at the same time in order to provide more evidence for the management of IgAN.

Subjects and methods

Research subjects

In Nephropathy Division, Fujian Medical University Union Hospital, we reviewed 288 adult patients (age ≥ 18) who had IgA nephropathy confirmed by biopsy from January 2016 to August 2018 (**Figure 1**). The inclusion criteria were as follows: (1) 18 years of age or older, male or female; (2) a diagnosis of IgAN based

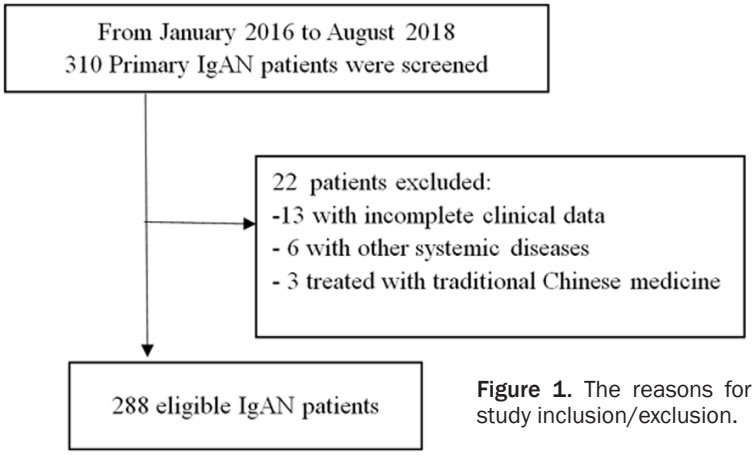

Figure 1. The reasons for study inclusion/exclusion.

on diffuse deposition of IgA-dominated immune complexes in the mesangial region detected by immunofluorescence and light microscopy; (3) not received corticosteroids, immunosuppressive agents and/or traditional Chinese medicine treatment before renal biopsy. The following exclusion criteria were used: (1) IgAN secondary to rheumatoid arthritis, Henoch-Schönlein purpura, chronic hepatitis B virus-associated glomerulonephritis; (2) patients combined with other glomerular diseases, such as diabetic nephropathy, and interstitial nephritis; (3) patients combined with systemic diseases such as diabetes, malignant tumor, severe infection, active tuberculosis, and autoimmune diseases; (4) patients with incomplete clinical and pathological data. The patients were excluded based on their clinical history, physical examination, and laboratory test results. The patients were divided into two groups: group A, symptomatic IgAN group (n = 146) and group B determined by physical examination (n = 142).

Outcome measures

Basic information: The basic information for patients such as gender, age, height, body weight, medical history and clinical presentations was collected.

Laboratory data: Urine examination was evaluated including routine urinalysis, 24-hour urine protein excretion, renal and liver function, blood glucose and lipid, electrolyte etc. Based on the severity of proteinuria, urine protein classifications were divided into level 0 (no proteinuria), level 1 (mild, proteinuria 0.15~1 g/day), level 2 (moderate, proteinuria 1 g/d~3 g/d) and level 3 (severe, proteinuria > 3 g/d). In addition, serum IgA, IgG, IgM, C3, C4 were detected. A simplified MDRD equation was used to calculate the estimated glomerular filtration rate (eGFR) [8].

Renal pathological data

Kidney pathology was performed by the Pathological Centre of Fujian Medical University using light microscopy, electron microscopy and immunohistochemistry examination. The pathological characteristics were graded from I to V according to the criteria of Lee SMK classification [9] and the Katafuchi R semi-quantitative evaluation method was also applied in lesions of renal glomerular, tubules and blood vessels [10].

Statistical analysis

The Data were analyzed by the software SPSS 18.0, with a significance level at $P < 0.05$. Using Student's t test and Chi-square test, the results of clinical characteristics and physicochemical indexes were compared between symptomatic and asymptomatic IgAN groups. The correlation between the level of proteinuria and pathological classification among IgAN patients was compared by Spearman rank correlation analysis. The result of the Katafuchi R semi-quantitative evaluation was compared by Wilcoxon rank sum test between the two groups. The deposition of antibodies and complements between the two groups was compared by Chi-square test. CKD classifications between the two groups were compared using Ridit analysis.

Results

Onset age and sex

The primary adult IgAN patients recruited consisted of 138 males (48%) and 150 females (52%), with a male to female ratio of 0.92:1. No significant difference in age distribution was found between the two groups (**Table 1**). Amongst all patients, 50 patients were identified and accompanied with the infectious diseases, including 40 with respiratory tract infection, 7 with urinary tract infection, 2 with gastroenteritis, and 1 with cholecystitis. BMI and body weight in group B were significantly

Table 1. The distribution of all ages in IgAN patients

Groups	< 20	20~30	30~40	40~50	> 50
A (n = 146)	10 (3.47%)	38 (13.19%)	43 (14.93%)	34 (11.81%)	21 (7.29%)
B (n = 142)	9 (3.12%)	39 (13.55%)	50 (17.36%)	30 (10.42%)	14 (4.86%)
Total	19 (6.59%)	77 (26.74%)	93 (32.29%)	64 (22.23%)	35 (12.15%)

Table 2. Comparisons in clinical characteristics between the two groups

Items	A (n = 146)	B (n = 142)	*P* (double)
Age (year)	36.29±11.57	35.34±10.75	0.47
Body weight (kg)	57.84±11.03	60.47±11.39	0.04*
Height (cm)	164.84±7.74	164.99±7.96	0.87
BMI (kg/m^2)	21.20±3.11	22.20±3.24	0.02*
With hypertension (%)	43 (14.90)	53 (18.40)	0.16

*$P < 0.05$.

Table 3. Comparisons in phsicochemical indexes between the two groups

Items	A (n = 146)	B (n = 142)	*P* (double)
Hb (g/l)	128.43±17.98	132.74±16.61	0.04*
ALB (g/l)	38.63±7.96	40.72±5.27	0.01*
CHOL (mmol/l)	5.22±1.85	5.18±3.18	0.89
BUN (mmol/l)	5.3 (2.3~35.2)	5.5 (2.1~51)	0.50
Scr (μmol/l)	110.66±93.27	93.27±66.28	0.10
GFR (ml/min/1.73 m^2)	89.04±47.19	95.47±71.72	0.37
URIC (μmol/l)	364.40±118.52	357.83±104.97	0.62
IgG (g/l)	11.45±3.26	12.26±2.40	0.02*
IgA (g/l)	3.06±1.06	3.38±0.99	0.01*
IgM (g/l)	1.40±0.79	1.32±0.52	0.30
C3 (g/l)	1.02±0.30	0.98±0.26	0.25
C4 (g/l)	0.27±0.18	0.24±0.09	0.06
IgA/C3	3.19±1.78	3.91±1.89	0.01*
Haematuria (/HP)	23.7 (0~906)	24.3 (0~1185.9)	0.78

*$P < 0.05$.

higher than those in group A, and other conditions between the two groups were not significantly different (**Table 2**).

Main laboratory indicators

Comparisons in physicochemical indexes: The main physicochemical indexes between two groups were compared in **Table 3**. The group B had significantly higher levels of serum ALB, IgG, IgA, IgA/C3 and blood Hb than group A ($P < 0.05$), while the other physicochemical indexes remained at similar levels in both groups ($P > 0.05$).

Comparisons in urine protein classifications: Comparisons in urine protein classification in IgAN patients were summarized in **Figure 2**. Most patients (112 cases, 38.89% of total cases) were classified into level 1, of which 20.83% were in Group A and 18.06% were in Group B. The percentage of patients with severe proteinuria in Group A appeared to be higher than that in Group B. However, such difference was not significant ($Z = -0.867$, $P = 0.39 > 0.05$).

Renal pathology

Comparisons in pathological classifications: The two groups were classified into I-V based on the pathological changes (**Figure 3**). No significant differences were found between the two groups ($Z = -0.107$, $P = 0.92 > 0.05$). Additionally, no distinct correlation with the severity of proteinuria was shown by the pathological classifications between IgAN patients (**Table 4**, Spearman coefficient = 0.009, $P = 0.06$).

Comparisons in Katafuchi R rating: The results were showed in **Table 5**, and the difference between two groups did not reach statistical significance ($P > 0.05$).

The characteristics of renal histopathological antibody and complement deposits among IgAN patients

No significant difference was found in renal antibody and complement deposits between the two groups (**Table 6**, $X^2 = 6.21$, $p = 0.54$).

Comparisons in CKD classification: The CKD classification in group A tended to be more seri-

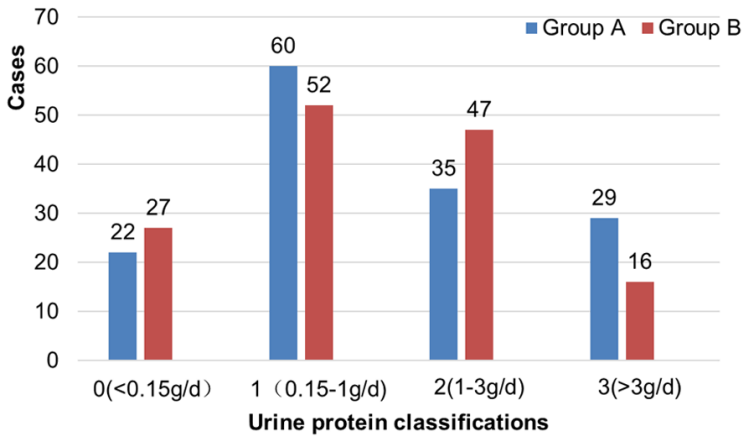

Figure 2. Comparisons in urine protein classifications between groups. Comparing the number of patients with different levels of proteinuria between the two groups, it was found that the number of patients with severe proteinuria in group A was more than that in group B, but there was no statistical difference between the two groups ($P > 0.05$).

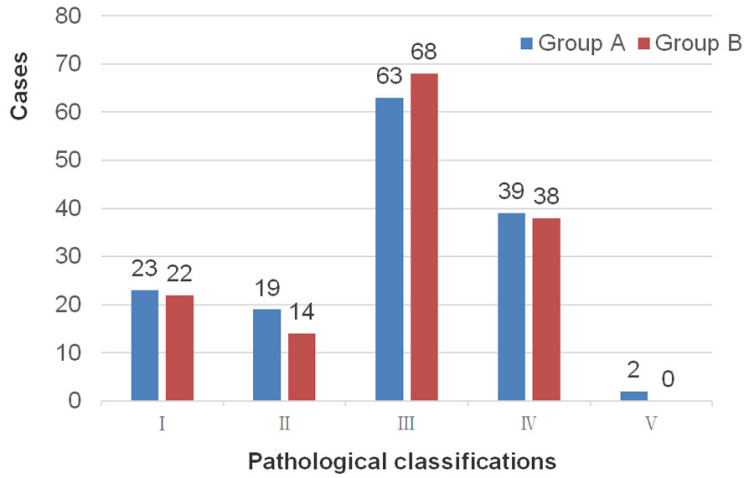

Figure 3. Comparisons in pathological classifications between groups. Comparing the number of patients in different pathological stages between the two groups, there was no significant difference in the number of patients between the two groups ($P > 0.05$).

ous than that in Group B, the number of IgAN patients in stage 3 to stage 5 in group A was greater than that in group B, however, no statistical significance was found for the difference between the two groups ($P = 0.08$, $Z = -1.751$) (**Table 7**).

Discussion

IgA nephropathy is the most common cause of chronic kidney disease in China. Most of IgAN patients found by physical examination did not exhibit obvious clinical symptoms. In our study, we had retrospectively analyzed 142 cases of asymptomatic IgAN patients which were found by physical examination, and had compared with 146 symptomatic patients at the same time in our department. Our data demonstrated that no significant differences were found in age, gender, height, blood pressure, urine protein, urinary RBC Counts, serum CREA, BUN, CHOL, URIC, IgM, C3, C4, eGFR and CKD classification between the two groups. However, the overall stages of CKD classification in the symptomatic group were relatively more serious, and patients in group A accounted for a larger proportion of stage 3 to 5 CKD than those in group B. But it could not be ignored that there were still quite a few cases with stage 3 to stage 5 CKD in group B. Therefore, we must pay attention to those patients with mild and even no clinical presentations.

Meanwhile, we had observed a significant reduction in blood Hb, serum albumin, serum IgA, IgG, IgA/C3, weight and BMI in the symptomatic group. Hb was decreased in patients with heavy renal pathological lesions, and it was regarded as the main clinical indicator to evaluate whether IgAN progressed [11]. Xie, et al. [12] also suggested Hb to be an independent risk factor to consider in evaluating and predicting the prognosis of IgAN. In our study, although the blood Hb remained in the normal range in both groups, the symptomatic group showed a significantly lower Hb range than that in the asymptomatic group. Overall, the decreasing Hb in IgAN patients might imply the disease progression and more severe renal pathologic lesions and this is verified by our data, too.

Similarly, the symptomatic patients had a lower level of serum albumin in comparison with

Table 4. Comparisons between proteinuria and pathological classifications among IgAN patients

Urine protein classifications	Pathological classifications n (%)					
	I	II	III	IV	V	Total
0 (< 0.15 g/d)	9 (3.13)	4 (1.38)	22 (7.64)	14 (4.86)	0	49 (17.01)
1 (0.15 g/d~1 g/d)	15 (5.21)	12 (4.17)	57 (19.79)	27 (9.38)	1 (0.35)	112 (38.89)
2 (1 g/d~3 g/d)	15 (5.21)	8 (2.78)	39 (13.54)	19 (6.60)	1 (0.35)	82 (28.47)
3 (> 3 g/d)	6 (2.08)	8 (2.78)	14 (4.86)	17 (5.90)	0	45 (15.63)
Total	45 (15.63)	32 (11.11)	132 (45.83)	77 (26.74)	2 (0.69)	288

Table 5. Comparisons in Katafuchi R rating between the two groups

Items	A (n = 146)	B (n = 142)	*P* (double)
Katafuchi R rating	7.80±4.43	7.85±3.89	0.92
Glomerulus	4.54±2.32	4.65±2.12	0.67
Tubular lument	2.88±1.99	2.96±1.95	0.75
Blood vessel	0 (0~6)	0 (0~2)	0.71

the asymptomatic patients. The serum albumin was also accepted as an independent risk factor in evaluating and predicting the prognosis of IgAN [12]. Therefore, in view of our observations, we speculated that decline of serum albumin in IgAN patients even still within the normal range might also imply the disease progression and the poor prognosis. To confirm the implications of serum albumin in IgAN, more studies are necessary.

The deposition of circulating immune complexes (CIC) in the glomerular mesangial area leads to chronic glomerulonephritis. Therefore, IgA nephropathy is considered to be an immune-mediated glomerulonephritis. This circulating immune complex is composed of galactose-deficient IgA1 (Gd-IgA1) and its autoantibodies [13]. The CIC analysis taken by patients with IgA nephropathy showed that immunoglobulin G was the main antibody [13]. Dong, et al. [14] found that serum IgG level was negatively correlated with deposition of glomerular IgG. A retrospective study of Liu, et al. [15] found that the lower the serum IgG level with IgA nephropathy, the higher the risk of adverse prognosis outcomes. The study also showed that serum IgG plays an independent predictive role in unfavorable renal outcomes. Our study found that the serum IgG level in group A was significantly lower than that in group B. It can be inferred that patients who have symptomatic IgA nephropathy are likely have more adverse prognosis.

The research conducted by Bonnet, et al. [16] showed that overweight might be an independent risk factor for progression of IgAN, and BMI is correlated with the degree of severe renal damage. Instead, in our research, the body weight and BMI in group B (asymptomatic patients) were significantly higher. The apparent discordance may be due to that the body weight and BMI among 288 IgAN patients in our study were all in the normal range. On the other hand, it meant that many cases found by physical examination were serious, too. But, the association between body weight and BMI with IgAN needs further clarification.

The significance of serum IgA, IgA/C3 in IgAN remains debated. Nam, et al. [17] found that patients with low level of serum C3 had a poorer kidney survival than those with high level serum C3, suggesting that serum C3 may be a valuable predictor for the progression of IgAN. Further, several studies indicated that IgA/C3 ratio gradually rose along with the progression of IgAN, reflecting the pathological severity of IgAN [18-20]. Komatsu, et al. [20] found that IgAN patients who have high serum IgA/C3 ratio (4.5 or higher) might have a poor prognosis. In our study, the two groups had the similar serum C3 level, and both were within normal range. Moreover, serum IgA and IgA/C3 levels in symptomatic group showed a significant decline, which is in contrary to the above studies. Therefore, more basic and clinical studies are needed to find the significance of serum C3 and IgA/C3 ratio in IgAN.

In renal pathology, depositions of immune complexes in mesangium are considered as a key factor in the pathogenesis of IgAN, and IgA deposits in mesangium are crucial for IgAN diagnosis. Additionally, C3 depositions are frequently observed in glomerular mesangium

Table 6. Comparisons in immunofluorescence antibody and complement deposits between groups

Groups	Features of renal histopathological immunohistochemical antibody deposits n (%)							
	A	A+C3	A+M	A+G	A+M+C3	A+G+C3	A+M+G	A+M+G+C3
A (n = 146)	12 (4.1)	14 (4.86)	6 (2.08)	2 (0.69)	33 (11.46)	4 (1.39)	11 (3.82)	64 (22.22)
B (n = 142)	11 (3.82)	8 (2.78)	13 (4.51)	2 (0.69)	35 (12.15)	6 (2.08)	6 (2.08)	61 (21.18)
Total	23 (7.99)	22 (7.64)	19 (6.59)	4 (1.38)	68 (23.61)	10 (3.47)	17 (5.90)	125 (43.40)

IgA, IgG, IgM were expressed in A, G, M, respectively.

Table 7. Comparisons in CKD classifications between the two groups

Groups	CKD classifications n (%)				
	1	2	3	4	5
A (n = 146)	67 (23.26)	42 (14.58)	25 (8.68)	7 (2.43)	5 (1.74)
B (N = 142)	75 (26.04)	46 (15.97)	15 (5.21)	3 (1.04)	3 (1.04)
Total	142 (49.31)	88 (30.55)	40 (13.89)	10 (3.47)	8 (2.78)

area along with IgG depositions [21]. In our study, the number of patients with C3 and IgG deposits accounted for 78.0% and 54% respectively, indicating that IgA often deposits in most IgAN patients along with C3 and IgG deposits. Komatsu, et al. [20] discovered that C3 deposits in glomerular mesangium were related to the severity of histological lesions in IgAN patients. Kim, et al. [22] also concluded that patients with higher C3 depositions had poorer renal lesions. However, it is not clear what kind of role complement activation plays in the IgAN progression and whether it impacts the long-term prognosis of IgAN [23].

Shin, et al. [24] found that the prognosis of IgA nephropathy patients with IgG deposition was more adverse than the patients without IgG deposition. Moreover, based on COX regression analysis, glomerular IgG deposition can be considered as an independent risk factor. Histological studies found that depositions of glomerular IgG are related to the progression of nephropathy, and patients with IgG deposition may have poorer prognosis [21, 24-26]. However, there were no differences in pathological grading and depositions of immune complexes between the two groups. Likewise, the difference in Katafuchi R rating was not observed between the two groups. Therefore we considered that renal pathology might be similarly serious in mild or even asymptomatic IgAN patients as those with obvious clinical manifestations and it needs more studies to prove.

Our data also showed that it accounted for a considerable proportion (42.0%) for IgAN patients with urine protein < 1 g/24 h, classified as Lee SMK III to V in renal pathology. European and American scholars suggest that renal biopsy is performed unless persistent proteinuria is more than 1 g/24 h. This may not be appropriate as some patients with mild clinical symptoms may have severe pathological changes by renal biopsy and therefore may lose the best treatment opportunity. Consequently, based on our data, we suggest that the renal biopsy should be taken in qualified hospitals for patients who have mild clinical presentations if there is no contraindication. This includes patients with persistent mild proteinuria (for example, < 0.5 g/24 h) or with glomerular hematuria only.

Conclusion

In conclusion, we propose that blood Hb, serum albumin and serum IgG level should be taken as primary indicators during the follow-up time of IgAN patients, and the decline of these indicators may reflect the disease progression and the poor prognosis despite that they may still be in normal range at early stage. In addition, severe renal histological damage can be observed in some IgAN patients with benign clinical features. We suggest to perform strict management for IgAN patients and renal biopsy timely. Besides, our data shows that significant decline of serum IgA and IgA/C3 in symptomatic IgAN patients compared to that of asymptomatic patients, which is contrary to other studies, so it needs furthermore research to confirm.

Disclosure of conflict of interest

None.

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