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ORIGINAL ARTICLE

The Value of Serum IgA in the Diagnosis, Clinical and Pathological Evaluation of Patients with IgA Nephropathy Found During Physical Examination in China

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SUMMARY

Background: **The goal was to study the role of serum IgA in patients with IgA nephropathy (IgAN) found during physical examination, and to explore its value in diagnosis, assessment of pathological injury, and clinical prediction of IgAN.**

Methods: **The study included 457 patients who were hospitalized between January 2010 and June 2018 due to physical abnormalities and diagnosed with kidney disease via renal biopsy. Renal histopathology was quantified according to Katafuchi semi-quantitative standards, while the IgAN patients were also scored according to Lee's grading system.**

Results: **The average age of the 457 patients was 39.62 ± 13.52 years when abnormalities were found during physical examination. IgAN (202 cases, 46.12%) was the most common type of primary glomerulonephritis in the 457 patients. Of the IgAN patients, 75.25% (152 cases) were under 45 years old at the time of abnormal physical examination and IgAN patients were significantly younger than non-IgAN patients. There was a significant difference in the gender ratio between IgAN patients and non-IgAN patients ($\chi^2 = 4.24$, $p = 0.039$). In IgAN patients, the proportion of male patients, serum creatinine (SCr), the glomerular lesion and tubulointerstitial scores, and serum IgA were statistically higher than in non-IgAN patients with other types of primary glomerulonephritis; however, MDRD-GFR was lower. The ROC curve of serum IgA in the diagnosis of IgAN showed the AUC was 0.602. One hundred forty-seven cases (72.77%) were Lee's III - V grade. The proportion of patients who were at Lee's III - V grades in the normal serum IgA group (184 cases) was higher than that of the elevated serum IgA group (18 cases). There were no significant differences in gross hematuria, proteinuria, MDRD-GFR, SCr, and hypertension between the two groups.**

Conclusions: **Serum IgA may be of little value in the diagnosis of patients with IgA nephropathy detected via physical examination. The level of serum IgA may have predictive value in evaluating Lee's pathological damage in IgAN patients.**

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KEY WORDS

IgA nephropathy, serum IgA, routine examination, histopathology, renal biopsy

INTRODUCTION

IgA nephropathy (IgAN) is one of the most common primary glomerular diseases worldwide, and it accounts for 30 - 40% of all biopsies in China [1]. IgAN is characterized as chronic and progressive, and prognoses are generally not optimistic. It is the leading cause of end stage renal disease (ESRD) in China, and nearly 30% of all IgAN patients will develop ESRD within 20 years after diagnosis [2,3]. The progression of IgAN depends primarily on the degree of histopathological injury of the kidney. Accurate assessment of pathological renal injury in IgAN is critical for clinical treatment and prognostic judgement and the diagnosis, assessment of pathological damage, and prediction of IgAN depend mainly on renal biopsies. However, as an invasive and traumatic examination, renal biopsy cannot be used as a routine and dynamic method, especially in some primary hospitals. Therefore, it is urgent to find evaluation indices that are more useful in the diagnosis and pathological evaluation of IgAN and, at the same time, are easy to perform in clinical practice. In recent years, IgAN research has focused on finding indicators for screening and early diagnosis [4]. The study of biochemical indicators in serum and/or urine of IgAN patients has earned much attention, with researchers suggesting that serum IgA is of great value in the diagnosis of IgAN before renal puncture [5] and should be used as an index to distinguish IgAN from non-IgAN [5-7]. Some patients with IgAN have elevated serum IgA levels, but others may have normal serum IgA levels. One of the issues addressed by the current study is to determine if there are differences in the clinical manifestation and renal pathological injury between patients with elevated serum IgA levels and patients with normal serum IgA levels. The present study enrolled biopsy-proven patients who were identified and diagnosed during physical examination. The aim is to understand the diagnostic value of serum IgA in IgAN by comparing the characteristics of serum IgA in patients with IgAN and without IgAN and to understand the significance of elevated serum IgA levels in IgAN by comparing the clinical and pathological data of patients with elevated serum IgA and normal serum IgA.

MATERIALS AND METHODS

Patients

We performed a retrospective analysis on the clinical and pathological data of patients hospitalized in the First Affiliated Hospital of Bengbu Medical College between January 2010 and June 2018 due to physical abnormalities and later diagnosed with kidney disease via renal biopsy. Exclusion criteria for this study were: (1) diabetic nephropathy; (2) lupus nephritis; (3) purpuric nephritis; (4) IgA nephropathy caused by blood system diseases; (5) kidney damage secondary to other systemic diseases such as hepatitis B, cirrhosis, or rheumatoid arthritis; (6) patients with malignant tumors or active pulmonary tuberculosis; (7) less than 10 glomeruli in renal biopsy tissue. All subjects were informed about this study which was approved by the ethics committee of the First Affiliated Hospital of Bengbu Medical College, and all participants signed informed consent forms prior to their inclusion in this study.

Laboratory parameters

Fasting venous blood (2 mL) was taken, without anticoagulation, from patients in the morning prior to renal biopsy. The normal range of serum creatinine (SCr) in the study is 44 - 115 μmol/L. Serum IgA was measured by immunoturbidimetry and the normal range of serum IgA was 0.7 - 4 g/L. Glomerular filtration rate (GFR) was estimated with the modified abbreviated MDRD equation [8]: MDRD-GFR = 186 x $[SCr]^{-1.154}$ x $[age]^{-1.154}$ x 1.233 x (0.742 if female).

Pathology parameters

Renal biopsy was performed by professional clinicians and technicians. Renal specimens were obtained by percutaneous puncture under ultrasound-guidance and were sent to Kingmed Diagnostics for immunofluorescence, light microscopy, and electron microscopy pathological examination. The deposition types and intensity of IgA, IgG, IgM, C1q, C_3, C_4, and fibrinogen were examined by direct immunofluorescence on frozen sections. Light microscopy specimens were imbedded in paraffin and stained with Schiff periodate (PAS), hematoxylin-eosin (HE), and Mason trichrome. Pathological diagnosis of each patient was made according to clinical and histological examination. All of the enrolled patients were estimated by Katafuchi semi-quantitative standards to calculate their glomerular, tubulointerstitial, and vascular lesion scores [9], for a total score of 0 - 41 points. The glomerular lesion score ranged from 0 - 26 points and included mesangial cell proliferation (0 - 3 points), mesangial matrix proliferation (0 - 3 points), crescent (0 - 8 points), adhesion (0 - 4 points), and glomerulosclerosis (0 - 8 points). The tubulointerstitial score was 0 - 9 points comprised of interstitial inflammatory cell infiltration (0 - 3 points), interstitial fibrosis (0 - 3 points), and tubular atrophy (0 - 3 points). The vascular score ranged from 0 - 6 points and included vascular thickening (0 - 3 points) and hyaline degeneration (0 - 3 points). Additionally, IgAN patients were classified as Lee's I - V according to Lee's grading system [10].

Statistical analysis

Continuous data were expressed as means ± SD and the *t*-test was used for comparisons between groups. Categorical data were expressed as counts and proportions,

Table 1. Comparison of the clinical and pathological indices of IgAN patients and non-IgAN patients.

	IgAN	non-IgAN
N	202	151
M/F	112/90 ▲	67/84
Age of physical abnormalities (year)	36.09 ± 11.74 △	42.10 ± 14.65
Age of renal biopsy (year)	37.23 ± 11.68 △	37.96 ± 9.28
Proteinuria (g/24 hours)	1.73 ± 1.78	2.17 ± 2.66
MDRD-GFR (mL/minute^{-1}/1.73 m^2)	81.77 ± 35.61 ▲	90.73 ± 42.46
SCr (μmol/L)	114.99 ± 90.61 △	98.56 ± 70.04
Hemoglobin (g/L)	133.15 ± 19.34 ▲	127.69 ± 21.40
Serum IgA (g/L)	2.78 ± 1.13 △	2.37 ± 0.98
Glomerular lesion score	8.40 ± 4.25 △	4.93 ± 4.08
Tubulointerstitial score	3.20 ± 1.89 △	2.42 ± 1.61
Vascular lesion score	0.99 ± 1.30	1.11 ± 1.33

Note: Comparison with non-IgAN group: ▲ $p < 0.05$, △ $p < 0.01$.

Table 2. Comparison between IgAN patients with elevated serum IgA and with normal serum IgA.

	Elevated group	Normal group
N	18	184
M/F	15/3 ▲	99/85
Age of physical abnormalities (year)	48.81 ± 12.41 △	34.85 ± 10.93
Age of renal biopsy (year)	50.11 ± 12.68 △	35.97 ± 10.82
Proteinuria (g/24 hours)	1.62 ± 1.41	1.74 ± 1.82
MDRD-GFR (mL/minute^{-1}/1.73 m^2)	79.26 ± 25.55	82.02 ± 36.50
SCr (μmol/L)	96.61 ± 33.36	116.78 ± 94.21
Hemoglobin (g/L)	135.89 ± 17.81	132.88 ± 19.51
Serum IgA (g/L)	4.89 ± 0.81 △	2.53 ± 0.75
Glomerular lesion score	7.83 ± 4.64	8.46 ± 4.22
Mesangial matrix hyperplasia score	1.11 ± 0.47 ▲	1.43 ± 0.62
Tubulointerstitial score	2.83 ± 2.09	3.24 ± 1.88
Vascular lesion score	0.78 ± 0.81	1.01 ± 1.34

Note: Comparison with non-IgAN group: ▲ $p < 0.05$, △ $p < 0.01$.

and the χ^2 value was calculated by Fisher's exact probability among groups. p-value < 0.05 indicated statistical significance. All statistical processing was performed using SPSS version 16.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Due to abnormal urine and/or renal function test results after physical examination, 457 patients were diagnosed as having kidney disease via renal biopsy. Among these patients, 202 were diagnosed with IgAN. The control group was comprised of 151 non-IgAN patients with

Table 3. Comparison of the Lee's grading between IgAN patients with elevated serum IgA and patients with normal serum IgA.

	Lee's					
	I	II	III	IV	V	Total
Normal group	9 (4.89%)	37 (20.11%)	78 (42.39%)	43 (23.37%)	17 (9.24%)	184
Elevated group	3 (16.67%)	6 (33.33%)	5 (27.78%)	3 (16.67%)	1 (5.56%)	18
Total	12	43	83	46	18	202

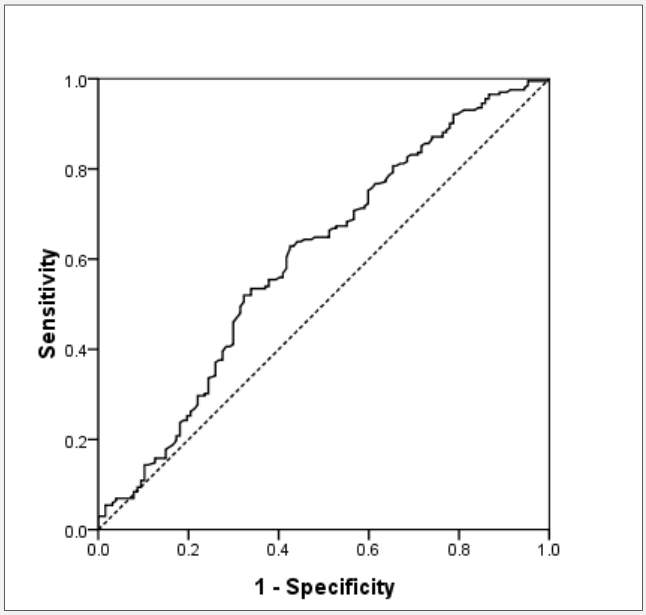

Figure 1. ROC curve of serum IgA in the diagnosis of IgAN.

other types of primary glomerulonephritis, including 41 cases of focal segmental proliferative glomerulonephritis (FSPGN), 31 cases of focal segmental glomerulosclerosis (FSGS), 28 cases of membranous nephropathy (MN), 36 cases of minimal change disease (MCD), and 15 cases of mesangial proliferative glomerulonephritis (MesPGN). IgAN (46.12%) was the most common type of primary glomerulonephritis in the 457 patients. Among the 457 patients, the average age at which abnormalities were found during physical examination was 39.62 ± 13.52 (range 6 - 75) years, and the average age at renal biopsy was 41.03 ± 13.48 (range 11 - 75) years. The median time from physical examination to renal biopsy was 3 months (range 3 days - 12 years). Of the IgAN patients, 75.25% (152 cases) were under 45 years old at the time of abnormal physical examination. The ratio of male:female in the IgAN group and non-IgAN group was 1.24 and 0.80, respectively. There was a significant difference in gender ratio between the two groups ($\chi^2 = 4.24$, $p = 0.039$). The percentages of CKD I, II, III, IV, and V stage were 45.05%, 26.24%, 19.80%, 5.45% and 3.47%, respectively. Table 1 shows that the IgAN patients were younger than non-IgAN ones, had higher levels of SCr, serum IgA, and hemoglobin, but lower MDRD-GFR. The ROC curve was analyzed for the diagnostic value of serum IgA in IgAN. The area under the curve (AUC) was 0.602, as shown in Figure 1. The glomerular lesion and tubulointerstitial lesion scores were higher in IgAN patients than in the control group.

The 202 IgAN patients were divided into two groups according to the upper value of serum IgA normal range

(4 g/L). As shown in Table 2, 184 (91.09%) patients had serum IgA levels in the normal range of 0.7 - 4 g/L and were designated as the normal group. The remaining 18 patients (8.91%) whose serum IgA were > 4 g/L were designated as the elevated group. There were statistically significant differences in sex, age, serum IgA, and mesangial matrix hyperplasia scores between the two groups. In the elevated group, the male proportion was higher, while patients in the normal group were younger and had higher mesangial matrix scores. There were no significant differences in the proportions of patients whose urinary excretion of protein > 3.5 g/24 hours, whose SCr > 115 μmol/L, and whose MDRD-GFR < 90 mL/minute/1.73 m^2. Meanwhile, the incidences of gross hematuria and hypertension in patients with elevated serum IgA were not significantly different from those in patients with normal serum IgA. Pathological lesions in the two groups were shown in Table 3. The number of patients who were at Lee's III - V grades was 138 (75%) in the normal serum IgA group which was higher than the number of patients (9 cases, 50.00%) in the elevated serum IgA group ($\chi^2 = 3.987$, $p = 0.046$).

DISCUSSION

IgAN is the most common type of primary glomerulonephritis [11,12] and, in the present study, accounted for 57.22% of primary glomerulonephritis cases in 44.20% of the 457 patients. The clinical manifestations of IgAN vary and can range from asymptomatic urine abnormalities, sometimes accompanied by proteinuria, to nephrotic syndrome and decreasing renal function. Most symptoms in IgAN are insidious at the onset and patients are often diagnosed during routine urine tests [13,14]. IgAN affects more than 1% of the average population [14]. In the present study, 75.25% of the IgAN patients were under 45 years old at the time of abnormal physical examination and the ratio of men to women was 1.24:1, which was higher than in the non-IgAN group. These results suggested that the majority of IgAN patients diagnosed during physical examinations are young adult males. According to Lee's grading system, 72.77% of the IgAN patients were assessed as Lee's grade III - V. Pathological injury was not mild in IgA patients detected during physical examination and, compared with the non-IgAN subjects, the glomerular and tubulointerstitial injuries were more serious and renal function was worse in IgA patients.

IgAN is a group of clinical diseases sharing the same immunopathological characteristics. The main feature of IgAN is the deposition of IgA or IgA-based immune complexes in the glomerular mesangial region. IgA deposits in the renal tissue of patients with IgAN derives mainly from blood circulation, and elevated serum IgA is associated with the onset of IgAN [15]. The present study showed that the mean serum IgA level in patients with IgAN was 2.78 g/L, which was significantly elevated compared to non-IgAN subjects. However, the ROC curve analysis revealed that serum IgA was of low diagnostic value in IgAN found during physical examination in China.

Gross hematuria has been confirmed as an indicator of active lesions in IgAN [16], and proteinuria has been proven as one of the determinants of poor prognoses in IgA nephropathy [17,18]. In addition, renal function and hypertension at the time of onset are also important risk factors in the prognosis of IgA nephropathy [19,20]. To further study the value of IgA in the pathological assessment and clinical prognosis of IgA nephropathy, the patients were divided into a normal group and an elevated group according to their serum IgA levels. Of the IgAN patients, 18 cases were delegated to the elevated serum IgA group, while 184 subjects presented with normal serum IgA levels. There were no significant differences in clinical presentation, such as proteinuria, renal function, gross hematuria or hypertension, between the two groups. We found that serum IgA may be of low value in the diagnosis and clinical assessment of IgAN, in contrast to previous studies [5-7]. The discrepancy may be due to differences in race, region, and pathological grading criteria. In addition, owing to the limited number of samples in this study, in particular as there were only 18 patients in the elevated serum IgA group, there may be statistical errors.

In order to characterize the pathological renal changes in the patients with IgA nephropathy, we evaluated pathology using the Katafuchi semi-quantitative standards and Lee's grading system. We found the normal serum IgA group had a higher degree of mesangial matrix hyperplasia than did the elevated level group. The Lee's grade is important for the prognosis of IgA nephropathy, and the Lee's grade III or above means a poor prognosis [21]. In this study, the proportion of patients who were at the grades of Lee's III - V in the elevated serum IgA group was lower. However, whether the prognosis of these patients is better than that of patients with normal serum IgA will be the future work in our follow up research.

CONCLUSION

In China, most of the IgA nephropathy patients diagnosed during physical examination are young and middle-aged men. Pathological changes are not mild in some patients and renal function were impaired. Serum IgA may be of little value in the diagnosis of IgA nephropathy. The level of serum IgA may have predictive value in evaluating Lee's pathological damage, and yet may have no predictive value in accessing the clinical condition. Clinicians should make overall considerations in light of the clinical manifestations of patients. It is necessary to conduct a renal biopsy early, which is very important for diagnosis and formulating individualized treatment plans in order to better protect renal function and delay the progression of IgAN.

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Declaration of Interest:
The authors had no potential conflicts of interest to declare in relation to this article.

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