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Original Article

IgA Nephropathy Associated with Acute Kidney Injury in Young Patients: The Clinicopathological Features and Risk Factors Analysis

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Abstract ***Objective:*** Little is known about the clinicopathological markers of IgA nephropathy (IgAN) to identify the acute kidney injury (AKI) among young patients. This work aimed to explore the possible risk factors of AKI. ***Methods:*** From 2012 to 2017, 110 patients aging from 2.5 to 16 with biopsy-proven primary IgAN were studied in our medical centre. The patients were divided into the AKI group (n=13) and the non-AKI group (n=97). ***Results:*** The occurrence of AKI among young patients with IgAN was 11.82% (13/110). Most AKI patients showed more proteinuria higher proneness to hypertension and higher content of uric acid. The proportion of glomeruli with crescents to the normal glomeruli was higher in the AKI group. The multivariate logistic regression analysis suggested that the elevated levels of proteinuria and uric acid might be the risk factors of AKI. ***Conclusion:*** AKI was common in young IgAN patients (age 2.5 - 16), who showed more severe clinicopathological symptoms than those without AKI. Some symptoms might be helpful in terms of determining the risk factors of AKI.

Key words *Acute kidney injury; Heavy proteinuria; IgA nephropathy; Risk factor; Uric acid*

Introduction

IgA nephropathy (IgAN) is one of the most common glomerulonephritis worldwide, especially among the Asian population. It is also the leading cause of the end-stage renal disease (ESRD) of patients with primary glomerular diseases.[1,2] Acute kidney injury (AKI) occurred in all age groups.[3] It has been reported that about 60% of the AKI patients could be fully cured during the post-acute stage, while 13.5% could be partially cured and 30% could not recover at all. The unrecoverable patients will gradually develop chronic kidney disease (CKD) and finally ESRD.[4] It normally takes 10 to 20 years for 20-30% IgAN patients to develop ESRD;[5-7] IgAN patients with AKI are more likely to develop CKD and ESRD.

The clinical and pathological symptoms of IgAN patients with AKI have not been fully studied, especially those of young patients. Previous studies of IgAN patients with AKI mostly focused on macroscopic haematuria.[8] Little is known about the determinative symptoms of AKI-IgAN and its risk factors. In order to explore this aspect in depth, 110 patients aging from 2.5 to 16 with biopsy-proven primary IgAN were studied in the Children's Hospital of Zhejiang University School of Medicine from 2012 to 2017, with both the clinical and pathological characteristics of IgAN associated with AKI recorded.

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Materials and Methods

Patients

The retrospective study data was recorded between January 2012 and January 2017 from 110 patients aging from 2.5 to 16 diagnosed with IgAN in the Nephrology Department of the Children's Hospital Zhejiang University

School of Medicine. Patients who were diagnosed with IgAN in other hospitals or with secondary IgAN (such as HSP, SLE and hepatitis B) were excluded from the study.

AKI was diagnosed upon the 2012 Kidney Disease: KDIGO criteria:[9] increase in SCr by 0.3 mg/dl (26.5 umol/l) within 48 h, or increase in SCr to 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days, or urine volume <0.5 ml/kg/h for 6h; serum creatinine (SCr) was used as the standard parameter in this study for determining the occurrence of AKI. First, the glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function. But it is difficult to measure and is commonly estimated from the serum level of endogenous filtration markers, such as creatinine. Creatinine is mainly excreted by glomerular filtration. When the intake of meat is stable and there is no significant change in muscle metabolism the creatinine production will be relatively constant;[9] second, according to 2012 Kidney Disease: KDIGO criteria, the definition of AKI is mainly determined by increase in SCr and urine volume. But young patients' urine volume is difficult to record and in this study these patients lacked relevant urine volume data. So SCr was used as the standard parameter here. We set the lowest value recorded between 3 months before the admission and the discharge date as baseline. If the SCr levels were elevated all the time mean SCr levels of healthy people in this age group were used as baseline. Venous blood samples of all the patients were taken to measure SCr immediately after admission. SCr of all patients was monitored at least once every week during hospitalisation. SCr was measured in micromoles per litre. Stratification of AKI also referred to the 2012 KDIGO guideline for clinical practice. Table 1 shows the staging of AKI.[9] In the present study there were 8 patients (61.54%) in the stage I, 4 (30.77%) in stage II and 1 (7.69%) in stage III.

These 110 patients underwent renal biopsy for the following reasons: (1) Unexplained AKI was found at admission or during hospitalisation, possibly accompanied by proteinuria or haematuria; (2) Gross haematuria (possibly accompanied by proteinuria) lasted for more than 2 weeks, excluding UTI; (3) Proteinuria lasted (>150 mg/d and <50 mg/kg/d) for more than 3 months without haematuria, excluding postural proteinuria. Patients with heavy proteinuria and decreased serum albumin were excluded from the data in the beginning. Each sample contained more than 10 glomeruli in renal specimen. The diagnosis of IgAN was based on the presence of IgA as the only or main immunoglobulin in the glomerular mesangial and the absence of systemic disease.

Clinical Data

Among the 110 patients studied, 13 matched the AKI criteria, making up the cumulative incidence of AKI 11.82%. The mean time taken from kidney biopsy to AKI occurrence was 4.46±2.03 days. Clinical data obtained from the original medical records of the patients included information on gender, age, levels of peak serum creatinine, uric acid, triglycerides, cholesterol, proteinuria (>50 mg/kg/24h) at the time of biopsy as well as the status of gross haematuria, anaemia and hypertension. Anaemia of patients in this study (2.5 years - 16 years) was defined by the following criteria:[10] (1) Children 6-59 months of age: Hb <110 g/l; (2) Children 5-11 years of age: Hb<115 g/l; (3) Children 12-14 years of age: Hb <120 g/l ; (4) Non-pregnant women (15 years of age and above): Hb <120 g/l. Men (15 years of age and above): Hb <120 g/l. Hypertension was defined according to the sex-age-height adjusted reference tables from Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[11] Some patients had incomplete medical information, such as urine volume and medication history before admission (especially the history of taking traditional Chinese medicine). So, we didn't have these statistics.

One of the 13 young patients with IgAN terminated his treatment and hence no further data were available. The remaining 12 patients were followed up for up to 72 months. All of the 12 patients recovered from the AKI within 3 months. No renal replacement treatment (RRT) was applied.

Pathological Data

Renal biopsy specimens were examined by light microscopy, electron microscopy and immunofluorescence and were graded according to the Oxford classification system and update[12-15] including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and cellular/fibrocellular crescents (C). Table 2 shows the recommendations for the interpretation of renal biopsy in IgA nephropathy.[15] Figure 1 shows different pathological images of patients in the AKI group and the non-AKI group.

Statistical Methods

Data was analysed using the SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). For continuous parameters, measurement results are reported as mean ± standard deviation (SD) for normal distribution or median with first and third quartiles for skewed distribution. For categorical

parameters, results were reported as frequency or percentage. Continuous data were compared by means of Student's t test; proportions were compared with chi-square test. Univariate logistic regression and multivariate logistic regression were used to determine probabilities of the occurrence. All p values were two-tailed, and $p<0.05$ was considered statistically significant.

Results

Clinical Features of Patients Between AKI Group and Non-AKI Group

Table 3 describes the clinical parameters of patients with and without AKI. Thirteen out of 110 patients (11.81%) were diagnosed with AKI. The 13 patients were made up of 10 male and 3 female patients with a mean age of 10.29± 2.67. Compared with non-AKI group, AKI group showed higher occurrence of heavy proteinuria (76.92% versus 24.74%, $p<0.001$) and hypertension (15.38% versus 0, $p=0.013$). The mean value of uric acid was also higher in AKI group than in non-AKI group (365.47±109.98 umol/L versus 273.33±73.67 umol/L, $p=0.011$). No significant differences were observed in other parameters.

Histopathological Features of Patients Between AKI Group and Non-AKI Group

Table 4 describes the histopathological parameters of patients with and without AKI. Compared with non-AKI group, more glomeruli with crescents were observed in AKI group ($p=0.022$). No significant differences were observed in other parameters.

Table 1 Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3 mg/dl (≥26.5 umol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 umol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Table 2 Recommendations for the interpretation of renal biopsy in IgA nephropathy

Detailed description of the features present on:
Light microscopy
Immunohistochemistry or immunofluorescence
Electron microscopy
Summary of 5 key pathologic features
Mesangial score <0.5 (M0) or >0.5 (M1)
Endocapillary hypercellularity absent (E0) or present (E1)
Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy / tip lesions in biopsy specimens with S1
Tubular atrophy / interstitial fibrosis 25% (T0), 26%-50% (T1), or >50% (T2)
Cellular / fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in >25% of glomeruli (C2)
Quantitative data
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, necrosis, extra capillary hypercellularity (cellular / fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis

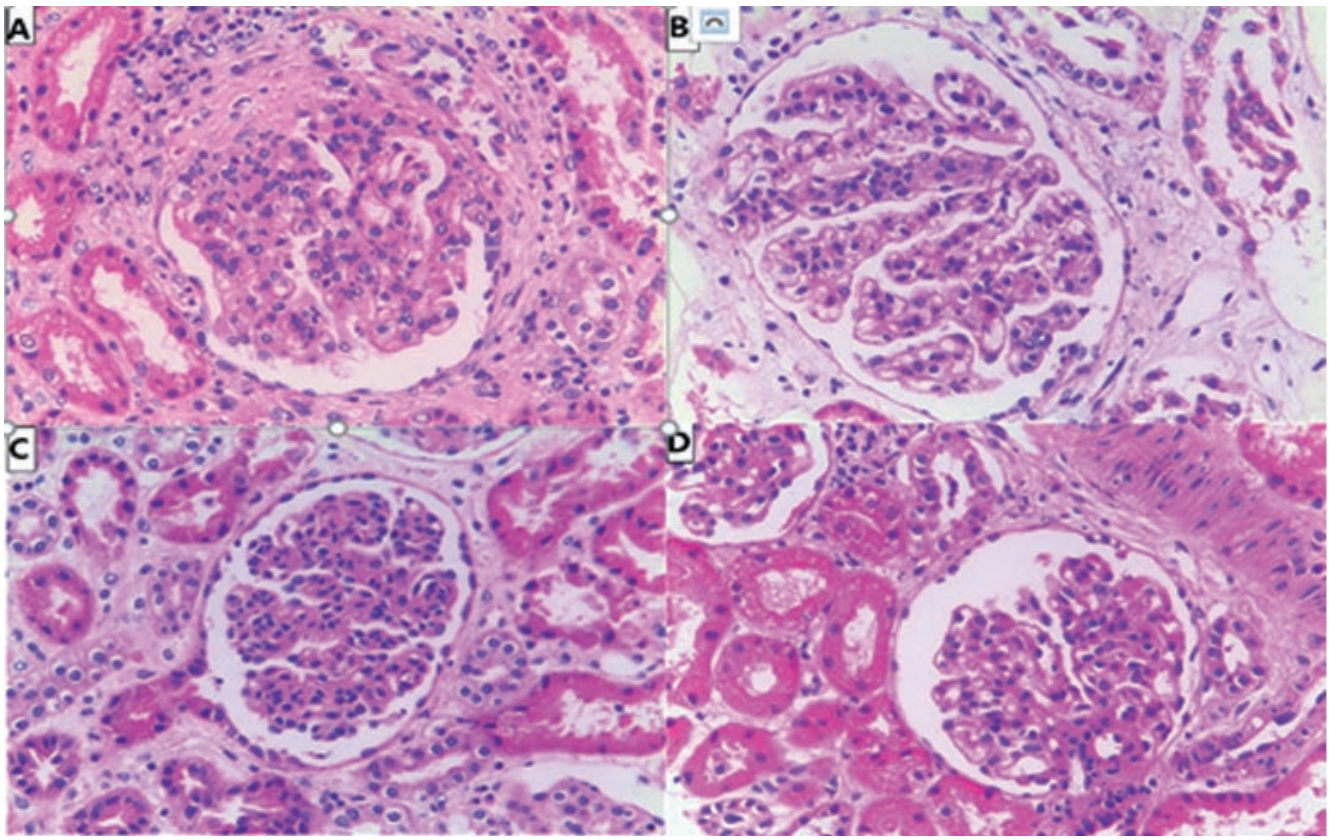

Figure 1 Different pathological images of patients in the AKI group and the non-AKI group. (A) A seven-year-old male patient with a high level of proteinuria and AKI (200x). (B) A thirteen-year-old male patient with a low level of proteinuria and AKI (200x). (C) A five-year-old female patient with a high level of proteinuria but without AKI (200x). (D) An eleven-year-old female patient with a low level of proteinuria and without AKI (200x).

Table 3 Comparison of clinical features between AKI and non-AKI group at the time of biopsy

Characteristics	AKI group (13)	Non-AKI group (97)	P values
Male gender (n, %)	10 (76.92)	58 (59.79)	0.363
Age (year)	10.29±2.67	9.57±2.97	0.404
Gross haematuria (n, %)	10 (76.92)	74 (76.29)	1.000
Heavy proteinuria (n, %)	10 (76.92)	24 (24.74)	<0.001
Hypertension (n, %)	2 (15.38)	0	0.013
Anaemia (n, %)	2 (15.38)	3 (3.09)	0.105
Peak SCr when AKI attack (umol/L)	115 (98.5, 113.95)	NA	NA
UA (umol/L)	365.47±109.98	273.33±73.67	0.011
TG (mmol/L)	1.62 (0.85, 1.94)	1.29 (0.95, 2.12)	0.435
CHOL (mmol/L)	4.59 (3.80, 7.68)	4.45 (3.88, 5.64)	0.787

Notes: SCr: serum creatinine; UA: uric acid; CHOL: cholesterol; TG: triglycerides; NA: not applicable; heavy proteinuria: 24-hour proteinuria greater than 50 mg per body weight per day. Data were reported as mean ± SD or median; categorical variables were reported as percentage.

The Associated Risk Factors With AKI

Table 5 shows the parameters associated with AKI among young patients with IgAN, analysed by the logistic regression. Heavy proteinuria (OR 16.867, 95% CI 2.144-132.725, p=0.007) and the content of uric acid (OR 1.016, 95% CI 1.006-1.027, p=0.002) were the most relevant parameters associated with AKI among young patients with IgAN.

Discussion

The definition of AKI has not been clearly defined until the release of 2012 KDIGO criteria. IgAN is the most diagnosed primary glomerular disease. IgAN patients with AKI are more likely to develop CKD and ESRD. In order to take precautions of AKI, clinicopathological symptoms and possible risk factors need to be learned. In this study, the occurrence of AKI among young patients with IgAN was 11.82%; the clinical and pathological information were also provided, availing an insightful understanding of the young IgAN patients with AKI. In this study it was found that AKI patients showed more notable clinical changes than non-AKI patients. Multivariate logistic regression analysis showed that the percentage of patients with heavy proteinuria and the level of uric acid differed the most between the two groups. The first conclusion is consistent with the previous study.[16] While hyperuricemia (HUA) caused by elevated uric acid levels (serum uric acid >420 umol/L for men and >350 umol/L for women) is a metabolic disease which could cause uric acid nephrolithiasis and gouty nephropathy. From the study of Hamid Nasri, uric acid played an important role in the pathological type and long-term prognosis of IgAN and it is an independent risk factor.[17] Xu et al conducted a systematic review and meta-analysis on HUA's risk of AKI, and conducted a randomised effect meta-analysis on a total of 75200 patients in 18 cohort studies. It was found that the high uric acid group had a higher risk of AKI than the control group (OR=2.24,95% CI:1.76~2.86, P<0.01), and the increased uric acid content was one of the risk factors for AKI.[18] Lapsia et al considered that with the increase of

Table 4 Comparison of pathological features between the AKI and the non-AKI group

Characteristics	AKI group (13)	Non-AKI group (97)	P values
Glomeruli with GS (n, %)	0	0	>0.05
Glomeruli with crescents (n, %)	6 (46.25)	16 (16.49)	0.022
M1 (n, %)	11 (84.61)	69 (71.13)	>0.05
E1 (n, %)	3 (23.07)	13 (13.4)	>0.05
S1 (n, %)	5 (38.46)	40 (41.23)	>0.05
T1 (n, %)	1 (7.69)	0	>0.05
T2 (n, %)	0	0	>0.05
C1 (0-25%cresents n, %)	5 (38.46)	16 (16.49)	>0.05
C2 (⩾ 25%cresents n,%)	1 (7.69)	0	>0.05

Notes: GS: global sclerosis. Data were reported as percentage.

Table 5 Risk factors of childhood AKI of the IgAN patients with univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Variables	OR	95%CI	P	OR	95%CI	P
Heavy proteinuria (n, %)	10.139	(2.576, 39.906)	0.001	16.867	(2.144, 132.725)	0.007
Uric acid (umol/L) mean±SD	1.013	(1.005, 1.020)	0.001	1.016	(1.006, 1.027)	0.002
Glomeruli with crescents (n, %)	4.339	(1.287, 14.627)	0.018	0.465	(0.065, 3.325)	0.446

Notes: Parameters with p<0.05 in univariate analysis for a relationship with AKI were entered into multivariate analysis as covariates.

uric acid content, the risk of AKI would also increase. A J-shaped relationship appears to exist between serum uric acid and AKI.[19] However, there is no uniform conclusion on the uric acid critical value for children and adolescents. Heavy proteinuria and hyperuricemia could help us assess the risk of AKI in IgAN patients, but they could not help us diagnose AKI.

There are three common causes of AKI: prerenal, renal and postrenal. Prerenal acute AKI is mainly caused by hypoperfusion injury, such as severe dehydration, shock, congestive heart failure, etc. Renal AKI could be caused by various primary and secondary kidney diseases, nephrotoxic drugs, poisons and renal vascular diseases. Postrenal AKI is mainly caused by obstruction. Besides, congenital malformation of the urinary system could also cause AKI. In this study, no congenital malformation of the urinary system was found; The patient's parents were unable to provide some accurate information about the patients, such as the premorbid medication history (especially traditional Chinese medicine) and urine output. So, we don't know exactly the causes of AKI of these patients.

It was reported in the previous study that age, gender, malignant hypertension and certain pathological characteristics such as glomerulosclerosis and cellular crescents were risk factors of AKI in IgAN patients.[20] However, there was no such relationship observed in this study. Some limitations might affect the results of this work: first, the retrospective study was single-centre and the sample size was small; second, SCr content was the only criterium for determining AKI, due to the lack of urine volume data; third, the pathological symptoms of young IgAN patients were relatively mild compared with adult IgAN patients (only one IgAN patient with AKI had over 25% crescents observed and no glomeruli with global sclerosis observed in this study).

Wald and co-workers followed up AKI patients and non-AKI patients for 3 years and found the risk for AKI patients to develop ESRD was 72 times higher than that for non-AKI patients.[21] In this study, none of the AKI-IgAN patients progressed to ESRD, possibly because the patients in this study were not seriously ill, thus not showing strong pathological symptoms.

At present, the pathogenesis of primary IgAN is not completely clear, and there is no specific treatment. Due to the diversity, recurrence, chronic progression and non-parallel clinicopathology of the clinical manifestations of this disease, there are few high-quality, multi-centre, randomised controlled clinical trials which have been ideal for clinical and renal pathological characteristics so far. Treatment options are mainly based on the main clinical manifestations and severity of renal disease. And the principles of multi-drug combination, low toxicity and long course of treatment are adopted. The main clinical drugs include adrenal glucocorticoids and various immunosuppressants, angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, fish oil and anticoagulants.[22] On the basis of referring to relevant clinical guidelines, our hospital has been learning and accumulating clinical experience in the treatment of IgAN in recent years. Therefore, treatment is not the focus of this study.

Conclusion

In this study, the overall occurrence of AKI in young IgAN patients was 11.81% (13/110). Heavy proteinuria and the uric acid content could be markers to help us diagnose AKI. When the 24-hour proteinuria of young patient is greater than 50 mg per body weight per day, the patient is more likely to have AKI; The higher the patient's uric acid level, the more likely the patient is to develop AKI.

Declaration of Interest

None

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