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Primary IgA nephropathy with nephrotic-range proteinuria in Chinese children

Jing-Li Zhao, Jing-Jing Wang*, Guo-Ping Huang, Chun-Yue Feng

Abstract

To investigate the clinicopathological features and outcomes of primary IgA nephropathy with nephrotic-range proteinuria in Chinese children. Patients with biopsy-proven IgA nephropathy and nephrotic-range proteinuria between January 2011 and December 2017 were included, and their proteinuria and renal function were followed up. A total of 90 patients were enrolled, and 21.1% (19/90) of them had decreased renal function at diagnosis. Complete remission, partial remission, and no response of proteinuria occurred in 88.6% (70/79), 10.1% (8/79), and 1.3% (1/79), respectively, of the 79 patients who were followed up for 6 to 104 months. 73.7% (14/19) of the patients with decreased renal function at diagnosis recovered to normal level while 26.3% (5/19) of them did not recover or progressed to end-stage renal disease. Two patients with normal renal function at diagnosis progressed to renal insufficiency during follow-up period. By multivariate analysis, the risk for renal function deterioration was significantly higher in the partial remission and no response groups than in the complete remission group. Remission of proteinuria was important for improving renal prognosis in children with IgA nephropathy and nephrotic-range proteinuria. The outcomes for pediatric patients appeared to be better than that reported in adults.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, C = crescent, CR = complete remission, CI = confidence interval, CTX = cyclophosphamide, E = endocapillary hypercellularity, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, HR = hazard ratio, IgAN = IgA nephropathy, M = mesangial hypercellularity, MCD = minimal change disease, MMF = mycophenolate mofetil, NR = no response, PR = partial remission, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis.

Keywords: IgA nephropathy, nephrotic-range proteinuria, Oxford classification, pediatrics

1. Introduction

IgA nephropathy (IgAN) is the most common form of glomerulonephritis and the leading cause of chronic glomerulonephritis worldwide today. It presents a highly variable course that includes a spectrum from a very mild disease to end-stage renal disease (ESRD). Studies have revealed that 20% to 50% of the patients with IgAN would progress to ESRD during a long-term follow-up period in adults.[1–3] For pediatric patients, it is reported that 11% of 241 Japanese children reached ESRD within 15 years.[4] In most of the IgAN patients, the initial manifestations are recurrent episodes of asymptomatic microscopic hematuria or gross hematuria that usually concurrent with infections, with or without proteinuria. Nephrotic-range proteinuria is a relatively rare presentation in IgAN, with a prevalence rate of 5% to 20%, and 7% to 30.6% in adults, and children,[5–9] respectively. However, persistent proteinuria has been identified to be one of the most important clinical risk factors for poor prognosis, as well as hypertension and renal insufficiency, while diffuse mesangial proliferation, segmental sclerosis, crescents (C), interstitial fibrosis, and tubular atrophy (T) are considered to be pathological risk factors.[10–13] So far, there are still few studies on the long-term outcomes of primary IgAN in children, especially those with clinical manifestation of nephrotic-range proteinuria. The purpose of this study is to investigate the clinical and pathological characteristics of primary IgAN patients with nephrotic-range proteinuria at diagnosis, their outcomes, and related factors in Chinese children, with a focus on proteinuria and renal function during follow-up period.

2. Patients and methods

2.1. Patients

This is an retrospective observational, single-center trial. Patients with biopsy-proven IgAN and nephrotic-range proteinuria between January 2011 and December 2017 at the Children's Hospital of Zhejiang University, Hangzhou, China were enrolled. All patients had definite pathological findings of mesangial hypercellularity (M) under light microscopy, predom-

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This study was approved by the Ethics Committee of Children's Hospital of Zhejiang University (ID 2019-IRB-123).

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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inantly mesangial deposition of IgA with 2+ on immunofluorescent staining and electron-dense deposits within the mesangium under electron microscopy. Exclusion criteria were as follows: congenital kidney disease or secondary IgAN such as Henoch–Schönlein purpura nephritis, hepatitis virus-associated glomerulonephritis, etc; hypertension; hyperuricemia; biopsy specimens containing fewer than 8 glomeruli.

2.2. Data collection and comparison

We obtained medical records containing information of gender, age at onset, clinical parameters at diagnosis (serum creatinine level, serum albumin level, serum uric acid level, hemoglobin, serum IgA level, 24 hours urinary protein excretion, blood pressure), treatments after diagnosis, follow-up duration, and outcomes of proteinuria and renal function during follow-up period. Estimated glomerular filtration rate (eGFR) of each patients was calculated. For each renal biopsy specimen, information on the number of glomeruli and the presence of M, endocapillary hypercellularity, segmental glomerulosclerosis, T, and C were collected and classified using the Oxford classification.[14–16] Additionally, outcome data for complete remission (CR), partial remission (PR), no response (NR), recovery or deterioration of renal function were recorded during follow-up period. The patients' characteristics were compared between the 2 groups of patients with normal and decreased renal function at diagnosis and during follow-up period, respectively.

2.3. Criteria and definitions

Nephrotic-range proteinuria was defined as 24 hours urinary protein excretion more than 40 mg/m^2/h or urinary protein to creatinine ratio over 2.0 g/g. Hypertension was defined as systolic or diastolic pressure that exceeded the 95th percentile on the basis of age-matched standard values. Hyperuricemia was defined as serum uric acid level over 420 μmol/L (male) or 360 μmol/L (female). eGFR was calculated according to the Schwartz formula,[17] and decreased renal function was defined as eGFR less than 90 mL/min/1.73 m^2. Observation period was defined as the time between diagnosis and the last outpatient clinic visit or telephone call, while it was defined as the time until initiation of renal replacement therapy in patients who developed ESRD. CR was defined as the absence of proteinuria, disappearance of clinical manifestations, normalization of biochemical findings, and no worsening of renal function. PR was defined as a more than 50% reduction in proteinuria from baseline to 40 mg/m^2/h. NR was defined as a less than 50% reduction or an increase in proteinuria or renal deterioration.

2.4. Statistical analyses

Continuous variables were described as mean ± standard deviation if they were normally distributed and compared with *t*-test. Nonparametric variables were expressed as median with range and compared with Mann–Whitney test. Categorical variables were described as number (%) and compared by χ^2 test or Yates' corrected χ^2 test or Fisher exact test between or among the groups. The Kaplan–Meier curve was used to illustrate the probability of CR, and comparisons were made with a log-rank test. Independent factors for CR and renal function deterioration were identified by univariate and multivariate analyses using Cox proportional hazards model. Statistical significance was determined as $P < .05$. SPSS software (version 23.0; SPSS Inc, Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Baseline characteristics

A total of 266 children were diagnosed with primary IgAN between January 2011 and December 2017 at our hospital, and 90 (33.8%, 90/266) of them presented with nephrotic-range proteinuria. Their baseline characteristics, which were stratified by renal function at diagnosis, are shown in Table 1.

3.2. Follow-up and outcomes of proteinuria and renal function

Because 11 patients were lost to follow-up, data of 79 patients were included in the follow-up period. Their characteristics are shown in Table 2. All but 2 of these patients received treatments of corticosteroids alone or combined with immunosuppressive

Table 1

Baseline clinical and laboratory characteristics of patients with IgAN and nephrotic-range proteinuria (n = 90).

	All patients (n = 90)	eGFR <90 mL/min/1.73 m^2 (n = 19)*	eGFR ≥90 mL/min/1.73 m^2 (n = 71)*	*P*
Age (yr)	8.4 ± 3.2	10.2 ± 3.1	7.8 ± 3.3	.002
Male sex, n (%)	64 (71.1%)	17 (89.5%)	25 (35.2%)	<.001
Laboratory tests				
Urinary protein excretion (mg/m^2/h)	129.3 ± 64.9	128.7 ± 81.9	129.6 ± 57.9	.97
Serum albumin (g/L)	26.5 ± 9.5	27.4 ± 9.8	26.2 ± 9.4	.65
eGFR (mL/min/1.73 m^2)	142.6 ± 38.9	73.4 ± 9.6	135.6 ± 31.6	.02
Hemoglobin (g/L)	126.6 ± 15.9	116.4 ± 17.8	129.9 ± 13.8	.03
Serum IgA (g/L)	2.0 ± 1.1	2.3 ± 1.5	1.9 ± 1.1	.47
Oxford classification, n (%)				
M1	88 (97.8%)	18 (94.7%)	70 (98.6%)	.38
E1	6 (6.7%)	3 (15.8%)	3 (4.2%)	.20
S1	43 (47.8%)	12 (63.2%)	31 (43.7%)	.13
T1	4 (4.4%)	4 (21.1%)	0 (0%)	<.001
C1 + C2	23 (25.5%)	9 (47.4%)	14 (19.7%)	.03

Data are expressed as mean ± SD or number of patients (%).

C = crescents, E = endocapillary hypercellularity, eGFR = estimated glomerular filtration rate, M = mesangial hypercellularity, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis.

* eGFR value of the baseline visit.

Table 2

Follow-up of renal function in patients with IgAN and nephrotic-range proteinuria (n = 79).

	All patients (n = 79)	eGFR <90 mL/min/1.73 m^2 (n = 7)*	eGFR ≥90 mL/min/1.73 m^2 (n = 72)*	*P*
Age (yr)	8.4 ± 3.4	10.1 ± 3.7	8.3 ± 3.4	.17
Male sex, n (%)	56 (70.9%)	5 (71.4%)	51 (70.8%)	.69
Baseline laboratory tests				
Urinary protein excretion (mg/m^2/h)	129.3 ± 64.9	161.9 ± 103.8	124.0 ± 57.3	.47
Serum albumin (g/L)	26.5 ± 9.5	21.0 ± 7.9	27.0 ± 9.5	.14
eGFR (mL/min/1.73 m^2)	114.3 ± 41.0	78.7 ± 9.0	116.9 ± 41.3	.12
Hemoglobin (g/L)	126.6 ± 16.0	105.0 ± 19.0	128.1 ± 14.7	.001
Oxford classification, n (%)				
M1	77 (97.5%)	7 (100.0%)	70 (97.2%)	1.00
E1	5 (6.3%)	3 (42.9%)	2 (2.8%)	<.001
S1	38 (48.1%)	6 (85.7%)	31 (43.1%)	.08
T1	4 (5.1%)	4 (57.1%)	0 (0.0%)	<.001
C1 + C2	19 (24.1%)	6 (85.7%)	13 (18.1%)	<.001
Follow-up duration (mo)	45 (6–104)	41 (26–104)	46 (6–103)	.40
Treatments, n (%)				
Corticosteroid alone	20 (25.3%)	0 (0.0%)	20 (27.8%)	
Corticosteroid + immunosuppressive agents	57 (72.2%)	7 (100.0%)	50 (69.4%)	
Nonsteroidal agents	2 (2.5%)	0 (0.0%)	2 (2.8%)	.23
Clinical response, n (%)				
Complete remission	70 (88.6%)	4 (57.1%)	66 (91.7%)	
Partial remission	8 (10.1%)	2 (28.6%)	6 (8.3%)	
No response	1 (1.3%)	1 (14.3%)	0 (0.0%)	.001

Data are expressed as mean ± SD or median (min-max/range) or number of patients (%).

C = crescents, E = endocapillary hypercellularity, eGFR = estimated glomerular filtration rate, M = mesangial hypercellularity, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis.

* eGFR value at the latest visit.

agents, which included cyclophosphamide, mycophenolate mofetil, and tacrolimus. Nonsteroidal agents included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, antiplatelet agents, and anticoagulant agents. For the 19 children who had decreased renal function at diagnosis, 6 and 12 cases were treated with corticosteroid alone and combination of corticosteroid and immunosuppressive agents, respectively, while 1 case was not treated with corticosteroid. Finally, 14 cases achieved recovery of renal insufficiency during the follow-up period while 5 cases failed (including 1 case of ESRD). Unfortunately, 2 patients with normal eGFR at diagnosis progressed to renal insufficiency during follow-up period. Renal insufficiency occurred significantly more often in the PR group ($P = .01$) and NR group ($P < .001$) than in the CR group. No significant difference was found in renal insufficiency between PR group and NR group ($P = .33$). Factors associated with CR and renal function deterioration were further investigated. Figure 1 shows the Kaplan–Meier analysis for the probability of CR

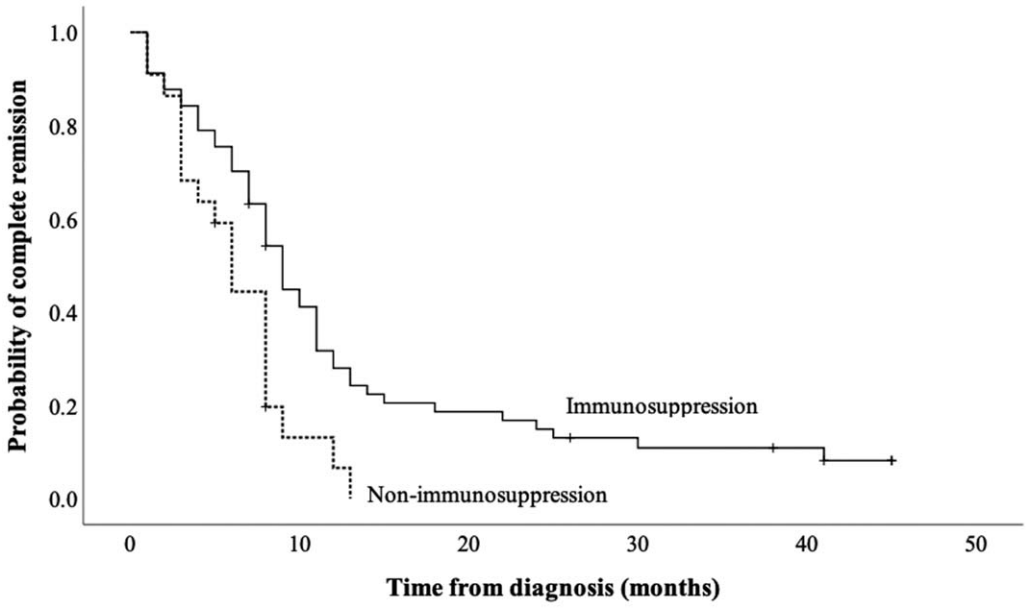

Figure 1. Kaplan–Meier plot showing the probability of complete remission stratified by immunosuppression treatment (log-rank $P = .004$).

Table 3

Cox proportional hazard model for prediction of complete remission in patients with IgA nephropathy and nephrotic-range proteinuria (n = 79).

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (male versus female)	1.52 (0.89–2.59)	.13	2.19 (1.18–4.09)	.01
Age (per 1 yr)	0.96 (0.90–1.03)	.23	0.94 (0.86–1.02)	.14
Renal insufficiency at diagnosis (versus normal renal function)	0.54 (0.29–1.02)	.06	0.81 (0.37–1.81)	.61
Baseline Alb <30 g/L (versus Alb ≥30 g/L)	1.46 (0.90–2.38)	.13	2.25 (1.22–4.13)	.01
Baseline proteinuria (per 1 g/m^2/24 h)	0.89 (0.75–1.05)	.15	0.91 (0.75–1.11)	.36
Oxford classification				
M1 (versus M0)	0.58 (0.14–2.41)	.46	1.80 (0.39–8.40)	.46
E1 (versus E0)	0.36 (0.11–1.17)	.09	0.61 (0.15–2.51)	.49
S1 (versus S0)	0.65 (0.40–1.05)	.08	0.84 (0.45–1.55)	.57
T1 (versus T0)	0.51 (0.16–1.65)	.26	0.48 (0.14–1.71)	.26
C1 + C2 (versus C0)	0.68 (0.38–1.23)	.20	0.90 (0.46–1.75)	.76
Immunosuppression treatment (versus non-immunosuppression treatment)	2.09 (1.21–3.62)	.01	2.30 (1.23–4.31)	.01

Renal insufficiency was defined as eGFR less than 90 mL/min/1.73 m^2.

Alb = albumin, C = crescents, CI = confidence interval, E = endocapillary proliferation, HR = hazard ratio, M = mesangial proliferation, S = segmental sclerosis, T = tubular atrophy/interstitial fibrosis.

stratified by immunosuppression treatment. By multivariate Cox regression analysis, albumin <30 g/L at diagnosis (hazard ratio [HR], 2.25; 95% confidence interval [CI], 1.22–4.13; $P = .01$), immunosuppression treatment (HR, 2.30; 95% CI, 1.23–4.31; $P = .01$), and male sex (HR, 2.19; 95% CI, 1.18–4.09; $P = .01$) were associated with a significantly increased likelihood of CR (Table 3), and the risk for renal function deterioration was significantly higher in the PR group (HR, 14.65; 95% CI, 1.06–201.88; $P = .04$) and NR group (HR, 86.24; 95% CI, 4.74–1567.75; $P = .003$) than in the CR group (Table 4).

4. Discussion

Nephrotic-range proteinuria is a relatively rare presentation but important risk factor for poor prognosis in IgAN patients. In our study, it showed that 33.8% of the children with primary IgAN have the clinical manifestation of nephrotic-range proteinuria, which is consistent with the result (30.6%) of a multi-center study in China,[9] but higher than that of other countries.[8] It may be partly because of racial or genetic differences, but still requires further study. We also found that it occurred more often in boys than girls, which is consistent with previous reports. Patients with decreased renal function at diagnosis showed significant lower eGFR and hemoglobin than those of the patients with normal renal function, indicating a more serious renal injury.

IgAN is a heterogeneous disease with different outcomes. Kim et al summarized 100 cases of adult IgAN patients with nephrotic-range proteinuria at diagnosis and reported that CR, PR, and NR occurred in 48%, 32%, and 20% of the patients,[7] respectively. In our experience, we found that 88.6% of the patients reached CR of proteinuria during the follow-up period. It seemed that pediatric patients with IgAN and nephrotic-range proteinuria had a better outcome than that reported in adult patients on considering the remission of proteinuria. Minimal change disease may be partially responsible for the development of nephrotic-range proteinuria in patients with IgAN, and corticosteroid therapy always leads to the resolution of proteinuria.[18–20] It was reported that the prognosis of some patients with IgAN and nephrotic syndrome was almost as good as that of those patients with minimal change disease.[7] In our

Table 4

Cox proportional hazard model for renal function deterioration in IgA nephropathy patients with nephrotic-range proteinuria (n = 79).

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (male versus female)	0.91 (0.17–4.95)	.91	1.58 (0.14–17.87)	.71
Age (per 1 yr)	1.29 (1.00–1.66)	.05	1.19 (0.90–1.57)	.22
Renal insufficiency at diagnosis (versus normal renal function)	0.01 (0.00–1330.67)	.34	0.01 (0.00–833.79)	.35
Oxford classification				
M1 (versus M0)	21.67 (0.00–6193.49)	.76	22.97 (0.00–8121.20)	.76
E1 (versus E0)	23.06 (3.78–140.70)	.01	5.79 (0.35–95.33)	.22
S1 (versus S0)	89.33 (0.11–7084.35)	.19	41.57 (0.06–3068.64)	.27
T1 (versus T0)	5.94 (0.66–53.35)	.11	3.00 (0.21–43.76)	.42
C1 + C2 (versus C0)	13.73 (1.56–120.88)	.02	5.99 (0.53–67.73)	.15
Nonsteroidal treatment (versus steroid treatment)	0.05 (0.00–8968.98)	.78	0.04 (0.00–1108.92)	.78
Clinical responses				
Complete remission	1.00 (reference)	NA	1.00 (reference)	NA
Partial remission	14.59 (2.82–347.57)	.01	14.65 (1.06–201.88)	.04
No response	31.33 (2.01–105.74)	.01	86.24 (4.74–1567.75)	.003

Renal insufficiency was defined as eGFR less than 90 mL/min/1.73 m^2.

C = crescents, CI = confidence interval, E = endocapillary proliferation, HR = hazard ratio, M = mesangial proliferation, NA = not applicable, S = segmental sclerosis, T = tubular atrophy/interstitial fibrosis.

study, albumin <30 g/L at diagnosis, immunosuppression treatment, and male sex were identified to be possible determinants for early CR. We considered that both nephrotic syndrome like manifestations (nephrotic-range proteinuria and hypoalbuminemia) at diagnosis and immunosuppression therapy promoted CR in those patients.

It is of interest that proteinuria and renal function during follow-up period were reported as the more powerful independent prognostic predictors, compared to those of the baseline level.[1,21–23] Previous research indicated that patients with nephrotic-range proteinuria at diagnosis who achieved CR during follow-up period had similar outcomes to patients with mild proteinuria at diagnosis, as well as superior prognoses to those who achieved PR or NR.[22] In our study, most of the patients achieved CR of proteinuria during the follow-up period, with a significant better renal prognosis than that of the PR group and NR group. For patients with decreased renal function at diagnosis, most of them achieved CR of proteinuria, and their renal functions recovered to normal level during follow-up period, while 1 child had sustained nephrotic-range proteinuria and she finally progressed to ESRD. Multivariate Cox regression analysis also revealed that the risk for renal function deterioration was significantly higher in the PR group and NR group than in the CR group. Our results were in line with those of previous studies, suggesting the importance of remission of proteinuria, to improve renal prognosis.[1,21–23]

Except for clinical factors, the effect of histological severity on renal injury had been emphasized by many studies, both in adults and children.[24–28] Consistent with the previous reports,[6,26] we found that pediatric patients showed more M and less chronic tubulointerstitial damage than adult patients. Nevertheless, differences of race, indication of renal biopsy, and experience of pathological evaluation should be taken into consideration. Lesions of T1 and C1 + C2 presented significantly more often in patients with decreased renal function than in those with normal renal function at diagnosis in our study, indicating higher scores of T and C were related to a more serious renal injury, which was consistent with the previous reports.[24–28] However, pathologic predictor for renal function deterioration was not identified in our study by multivariate Cox regression analysis.

For pediatric patients with IgAN and nephrotic-range proteinuria, boys have a higher prevalence than girls, with pathological characteristics of more M and less tubulointerstitial lesions than adults. Albumin <30 g/L at diagnosis, corticosteroid treatment, and male sex might be the possible determinants for CR in children with IgAN and nephrotic-range proteinuria. We emphasize the importance of remission of proteinuria in improving renal outcomes. Thankfully, the outcomes for pediatric patients seemed to be not so serious as that reported in adults.

Our study could help to learn more about primary IgAN in Chinese pediatric patients with clinical manifestation of nephrotic-range proteinuria to some extent. However, we were aware of several limitations of our study. First, it was a single-center study with a small sample size, and it was not a randomized controlled trial, which might lead to bias. Second, all of the pathological findings were obtained at diagnosis other than the period when the disease activity became high during the follow-up period. Therefore, multi-center studies with large sample sizes are needed to verify these results in the future.

Author contributions

Conceptualization: Jing-Jing Wang.
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Supervision: Jing-Jing Wang.
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Writing – review & editing: Jing-Li Zhao, Jing-Jing Wang, Guo-Ping Huang, Chun-Yue Feng.

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