ORIGINAL ARTICLE

Spontaneous remission in children with IgA nephropathy

**Yuko Shima · Koichi Nakanishi · Taketsugu Hama ·
Hironobu Mukaiyama · Hiroko Togawa ·
Mayumi Sako · Hiroshi Kaito · Kandai Nozu ·
Ryojiro Tanaka · Kazumoto Iijima ·
Norishige Yoshikawa**

Abstract

Background Some patients with IgA nephropathy (IgAN) achieve spontaneous remission even when not receiving medication. However, details on such remissions remain unknown. The aim of our study was to clarify this information in the clinical setting of childhood IgAN with minor glomerular abnormalities or focal mesangial proliferation (MGA/FMP).

Methods This study was a retrospective analysis of 96 children with MGA/FMP who did not receive medication from among the 555 patients with newly diagnosed childhood IgAN treated between January 1972 and December 2000. The Kaplan–Meier method and Cox proportional hazard model were used for the analysis.

Results Of the 96 pediatric patients who did not receive medication, 57 (59.4 %) achieved spontaneous remission. The cumulative spontaneous remission rates among these patients were 57.5 and 77.4 % at 5 and 10 years, respectively, from onset. The mean time from onset to remission was 5.9±0.4 years. Clinical and histological findings were similar between the remission and non-remission groups. Of the 57 patients with spontaneous remissions, ten (17.5 %) also developed a recurrence of urinary abnormalities. The cumulative recurrence-free rates were 79.9 and 67.9 % at 5 and 10 years, respectively, after remission.

Conclusions The spontaneous remission rate in childhood IgAN with MGA/FMP was higher than expected. Our results suggest that physicians should consider the potential for spontaneous remission and refrain from very aggressive treatment in IgAN patients with MGA/FMP.

Keywords Minor glomerular abnormality · Focal mesangial proliferation · Recurrence · Kaplan–Meier method · Cox proportional hazard model

Y. Shima · K. Nakanishi (✉) · T. Hama · H. Mukaiyama ·
H. Togawa · N. Yoshikawa
Department of Pediatrics, Wakayama Medical University,
811-1 Kimiidera,
Wakayama City, Wakayama 641-8509, Japan
e-mail: knakanis@wakayama-med.ac.jp

M. Sako
Division for Clinical Trials,
National Center for Child Health and Development,
Setagaya,
Tokyo, Japan

H. Kaito · K. Nozu · K. Iijima
Department of Pediatrics,
Kobe University Graduate School of Medicine,
Kobe, Hyogo, Japan

R. Tanaka
Department of Nephrology,
Hyogo Prefectural Kobe Children's Hospital,
Kobe, Hyogo, Japan

Introduction

Immunoglobulin A nephropathy (IgAN) is currently the most common type of primary glomerulonephritis worldwide. Long-term follow-up studies have revealed that the disease progresses to renal failure in 20–50 % of adult patients over 20 years [1]. Due to the variability in and the severity of glomerular manifestations, as well as a long disease duration, determination of the optimal treatments for patients with IgAN have remained elusive [1, 2]. A study of 241 Japanese pediatric patients revealed that 11 % of the patients developed end-stage renal disease (ESRD) within 15 years [3]. In another study, children with diffuse (>80 %) mesangial proliferation on renal biopsy were reported to be

at a high risk for renal insufficiency, with 17 % progressing to ESRD [4].

Conversely, some patients with IgAN, especially those showing minor glomerular abnormalities or focal mesangial proliferation (MGA/FMP), achieve spontaneous remission while not receiving medication. However, details regarding the incidence of and prognostic factors for remission remain unknown. The aim of this study was to clarify the incidence of spontaneous remission in childhood IgAN with MGA/FMP and identify the relevant prognostic factors.

Methods

Patients

The study protocol was based on the Declaration of Helsinki and approved by the Wakayama Medical University research ethics vetting boards. The medical cases of children under 20 years of age who had undergone routine renal biopsy at Kobe University and Wakayama Medical University hospitals between January 1972 and December 2000 were retrospectively analyzed. Only the cases of patients with IgAN who had not received medication for the entire follow-up period were selected for review. The diagnosis of IgAN was based on the presence of IgA as the sole or predominant immunoglobulin in the glomerular mesangium in the absence of systemic disease [5]. MGA/FMP and diffuse mesangial proliferation (DMP) were defined on the basis of the World Health Organization criteria. That is, DMP was defined as >80 % of glomeruli showing moderate or severe mesangial cellular proliferation, i.e. more than three cells per peripheral mesangial area [6]. The diagnosis of IgAN for all participants was confirmed by a single investigator (NY) using the same criteria throughout the entire study period. Renal biopsy was performed in children with persistent proteinuria with or without hematuria (defined in detail below). Patients with a follow-up duration of <12 months were excluded.

Data set

A spontaneous remission was defined as a normalization of urine (no hematuria and proteinuria) in a patient who was not receiving medication, including anti-hypertensive drugs. Hematuria was defined as five or more red blood cells in a properly collected and centrifuged urine specimen examined under a high-power field. Proteinuria was defined as either a positive dipstick reading of ≥ 1, daily urinary protein amount of ≥ 0.1 g/m^2/day, or a urinary protein/creatinine ratio of ≥ 0.2 g/g. Heavy proteinuria was defined as a daily protein amount of >1.0 g/day per 1.73 m^2 or a urinary protein/creatinine ratio of >1.0 g/g. The estimated glomerular filtration rate (eGFR) was determined using the Schwartz formula with the constants 0.55 and 0.7 for adolescent boys [7]. Renal insufficiency was defined as stage III and IV chronic kidney disease (CKD; eGFR <60 ml/min/1.73 m^2) [8], as stage III CKD is recognized as "irreversible." ESRD was defined as stage V CKD (eGFR <15 ml/min/1.73 m^2 or requiring renal replacement therapy).

Statistical analyses

Data were analyzed with the JMP ver. 9 software package (SAS Institute, Cary, NC). Normally distributed data were expressed as the mean ± standard deviation (SD), and non-parametric data were expressed as the median and interquartile range. With the exception of mesangial proliferation, histological data were expressed as the number and range due to low prevalence. Continuous data were compared using the Mann–Whitney U test, and categorical data were compared using Fisher's exact test. Cumulative event rates were calculated using the Kaplan–Meier method. The Cox proportional hazard model was used to identify prognostic factors for spontaneous remission. Factors related to spontaneous remission were carefully selected based on clinical importance. All P values were two-tailed, and P values of <0.05 were considered to be statistically significant.

Results

Patients

Patient characteristics are presented in Fig. 1. A total of 555 children, aged less than 20 years, were newly diagnosed as having biopsy-proven primary IgAN between January 1972 and December 2000. As shown in Fig. 1, 248 of the 376 patients with IgAN showing MGA/FMP (66.0 %) were treated with medication during their clinical courses. Of the 128 patients with IgAN who received no medication, data were available for 96, and the cases of these patients were retrospectively analyzed.

Spontaneous remission

Of the 96 patients not receiving medication, 57 (59.4 %) achieved spontaneous remission. Thus, of the 555 newly diagnosed biopsy-proven primary IgAN cases meeting the inclusion criteria, at least 57 (10.3 %) had spontaneous remission. The mean observation period was 9.6±4.3 years in the remission group and 5.8±4.1 years in the non-remission group (P<0.001). Since the duration of follow-up was different among patients, we used the Kaplan–Meier method to evaluate spontaneous remission. As shown in Fig. 2, the cumulative spontaneous remission rates, as
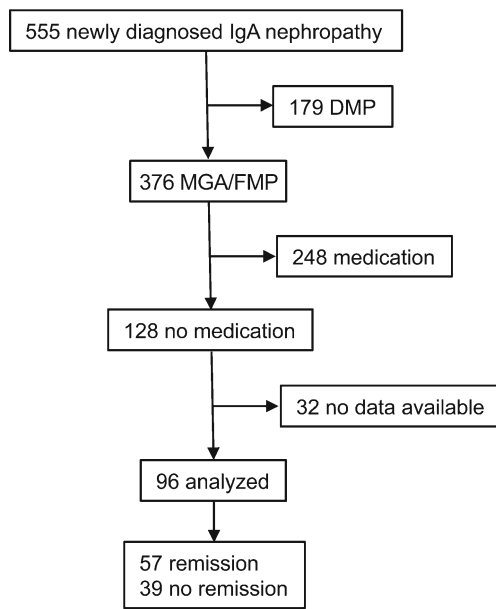
Fig. 1 Patient characteristics. *IgAN* immunoglobulin A nephropathy, *DMP* Diffuse mesangial proliferation, *MGA/FMP* minor glomerular abnormality or focal mesangial proliferation

determined by the Kaplan–Meier method, were 57.5 and 77.4 % at 5 and 10 years, respectively, from onset. The mean time from onset to remission was 5.9±0.4 years. A longer than 5-year duration of remission was confirmed in 28 of the 57 patients with spontaneous remission (49.1 %).

Compared to the clinical findings, there were significant differences in age at biopsy, duration from onset to biopsy, and duration from biopsy to the latest observation between the remission group and the non-remission group (Table 1). Histological analyse revealed significant differences in glomeruli showing mesangial proliferation, global sclerosis, and segmental sclerosis between the groups (Table 1). Table 2 presents the results of analyses using the Cox proportional hazard model on potential contributory factors for spontaneous remission. Only global and segmental sclerosis were significant in both the unadjusted and adjusted analyses, although prevalence of lesions was not high.
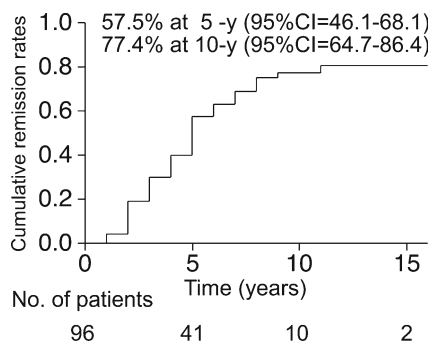

Fig. 2 Kaplan–Meier plot of the cumulative spontaneous remission rates in children with immunoglobulin A nephropathy showing minor glomerular abnormality or focal mesangial proliferation. *CI* Confidence interval

Since some patients had a recurrence of urinary abnormalities after spontaneous remission, we analyzed their state of recurrence. Of the 57 patients with spontaneous remission, ten patients (17.5 %) had a recurrence of urinary abnormalities. As shown in Fig. 3, cumulative recurrence-free rates after remission, as determined by the Kaplan–Meier method, were 79.9 and 67.9 % at 5 and 10 years, respectively, from the remission. The mean time from remission to recurrence was 7.6±0.4 years.

Outcome at the latest follow-up

The mean observation period of the entire cohort was 8.0± 4.6 years (range 1.0–18.9 years). The number of patients with normal urinalysis, hematuria only, slight proteinuria, and heavy proteinuria were 49 (51.0 %), 15 (15.6 %), 29 (30.2 %), and 2 (2.1 %), respectively, at the latest follow-up of the 96 patients with IgAN not receiving medication. Owing to the study design, where only patients not receiving medication were selected, 93 (96.9 %) of the 96 patients progressed into an improved clinical condition. However, one patient suddenly developed ESRD at 11 years from onset. She did not achieve spontaneous remission and had slight proteinuria continuously until 10 years from onset. The reason for the sudden deterioration in renal status remains unknown.

Discussion

Persistent proteinuria is currently considered to be a risk factor for the progression of renal disease, even in children with IgAN and MGA/FMP and, therefore, such cases warrant treatment [9]. Physicians sometimes recognize spontaneous remission in patients with IgAN, but the true incidence remains unknown. Thus, our study may provide unique and valuable data regarding spontaneous remissions in patients with IgAN.

In our study, to avoid patient selection bias and obtain accurate information, we first reviewed the medial cases of all children with biopsy-proven primary IgAN during the study period. We identified 555 pediatric patients who fulfilled these criteria, of whom 96 (17.3 %) did not receive medication and had adequate data available.

One major finding of our study is that a considerable proportion of patients with IgAN and MGA/FMP achieved spontaneous remission. As many as 57 (59.4 %) of the 96 patients who did not receive medication surprisingly underwent spontaneous remission, suggesting that at least 57 of the total 555 (10.3 %) children with biopsy-proven IgAN had spontaneous remission.

In terms of the clinical characteristics of our study population, there was a significant difference in the duration

Table 1 Characteristics of children with immunoglobulin A nephropathy according achievement/non-achievement of spontaneous remission

Patient characteristics	Remission (n=57)	Non-remission (n=39)	P
Clinical findings			
Sex (n, male/female)	36/21	24/15	0.99
Onset age (year)	9.6±3.0	11.0±2.8	0.10
Onset mode, n (%)			0.59
Hematuria	9 (15.8)	9 (23.1)	
Hematuria + proteinuria	24 (42.1)	13 (33.3)	
Proteinuria	3 (5.3)	4 (10.3)	
Gross hematuria	21 (36.8)	13 (33.3)	
Age at biopsy (year)	11.0±3.0	12.5±2.7	0.02
Duration from onset to biopsy (median, year) [range 25–75 %]	0.5 [0.3–1.8]	1.1 [0.6–2.3]	0.045
State at biopsy, n (%)			0.31
Hematuria	21 (36.8 %)	10 (25.6 %)	
Slight proteinuria	32 (56.1 %)	28 (71.8 %)	
Heavy proteinuria	4 (7.0 %)	1 (2.6 %)	
Systolic blood pressure (mmHg)	108±12	110±10	0.16
Diastolic blood pressure (mmHg)	61±10	64±11	0.11
Urinary protein excretion (median, g/m^2/day) [range, 25–75 %]	0.55 [0.10–1.00]	0.25 [0.10–0.53]	0.20
Gross hematuria (n, yes/no)	39/18	27/12	0.99
Estimated GFR (ml/min/m^2)	97±24	109±29	0.09
Serum IgA (mg/dl)	258±107	296±120	0.11
Duration from biopsy to latest observation (year)	7.7±3.7	4.1±3.2	<0.001
Histological findings			
Mesangial proliferation (median, %)	15.4	27.3	0.02
Range [25–75 %]	[1.4–27.9]	[13.9–48.9]	
Crescents (n, no/yes)	38/19	21/18	0.29
Range [%]	[0.0–20.0]	[0.0–20.0]	0.27
Capsular adhesions (n, no/yes)	47/10	29/10	0.44
Range [%]	[0.0–18.2]	[0.0–16.7]	0.32
Global sclerosis (n, no/yes)	54/3	31/8	0.046
Range [%]	[0.0–8.3]	[0.0–11.1]	0.02
Segmental sclerosis (n, no/yes)	57/0	35/4	0.02
Range [%]	[0.0–0.0]	[0.0–40.0]	0.02
Tubular atrophy[a] (n, no/yes)	33/24	18/21	0.30
Range	[0–1+]	[0–1+]	
Interstitial infiltration[a] (n, no/yes)	46/11	32/7	0.99
Range	[0–1+]	[0–2+]	
Endocapillary proliferation[b] (n, no/yes)	26/19	15/9	0.80
Range [%]	[0.0–28.6]	[0.0–14.3]	0.44
Intensity of mesangial IgA deposits[c]	2.5±0.7	2.2±0.7	0.051

IgA, Immunoglobulin A, GFR glomerular filtration rate

Data are expressed as the mean ± standard deviation (SD), unless indicated otherwise

[a] The intensity of tubular atrophy and interstitial findings were graded semi-quantitatively on a scale from 0 to 3+, where 0=no, 1+=slight, 2+=moderate, and 3+=intense.

[b] The total patient number is 69

[c] The intensity of deposits as determined via immunofluorescence microscopy was graded semi-quantitatively on a scale from 0 to 3+, where 0=no, 1+=slight, 2+=moderate, and 3+=intense

from biopsy to latest observation between the remission and non-remission groups. Several interpretations can be deduced from this finding. One reason for this may be that the longer observation period in the remission group

Table 2 Cox proportional hazard model of factors associated with spontaneous remission in children with IgA nephropathy ($n=96$)

Potential factors affecting spontaneous remission	Unadjusted		Adjusted[a]	
	Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P
Age at biopsy (per year)	0.94 (0.86–1.02)	0.12	0.98 (0.89–1.01)	0.67
Duration from onset to biopsy (per year)	0.79 (0.64–0.93)	0.004	0.85 (0.68–1.03)	0.067
Duration from biopsy to latest observation (per year)	1.04 (0.97–1.12)	0.29	1.02 (0.95–1.11)	0.54
Mesangial proliferation (per 1 %)	0.99 (0.98–1.01)	0.24	0.99 (0.98–1.01)	0.68
No crescents (vs. yes)	0.97 (0.56–1.72)	0.90	0.90 (0.49–1.68)	0.72
No global sclerosis (vs. yes)	3.11 (1.15–12.79)	0.02	3.19 (1.01–14.17)	0.047
No segmental sclerosis (vs. yes)	5.13×10^5 (2.45–NA)	0.003	3.20×10^5 (1.40–1.32×10^{149})	0.02

95 % CI, 95 % confidence interval; NA, not available

[a] Adjusted for age at biopsy, duration from onset to biopsy, duration from biopsy to latest observation, mesangial proliferation, crescents, global sclerosis, and segmental sclerosis

reflected the bias inherent to a retrospective study. Another explanation may be the possibility that there were changes in disease severity during the study period, which would suggest that the milder cases were diagnosed via a renal biopsy during the earlier period. Additionally, there may be slight inconsistencies in the biopsy criteria. However, there were no statistical differences in the status at biopsy between the remission and non-remission groups (Table 1). Another possibility may be differences in medication selection, in particular, the ratio of patients taking no medication. With respect to the date of diagnosis in the 96 patients, 59, 36, and one patient were diagnosed in the 1970s, 1980s, and 1990s, respectively. The ratio of patients with IgAN not receiving medication clearly decreased over time, which may be associated with the wide use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in Japanese children with proteinuria and MGA/FMP since the beginning of the 1990s [9, 10].

The cohort analyzed in our study appears to consist of patients with mild disease. Therefore, due to the very narrow spectrum of severity, it was expected that it would be difficult to detect a significant factor for spontaneous remission. In fact, we found that only global and segmental sclerosis were significant factors in both the unadjusted and adjusted analyses. These findings suggest the possible importance of these lesions. However, the prevalence of both types of histological lesions was not high. Therefore, care should be taken in estimating the value of lesions.

In clinical practice, the possibility of a recurrence of disease in IgAN patients should be always be considered. We found that even after spontaneous remission, a proportion of patients had a recurrence of disease. The mean time from remission to recurrence was 7.6 years, as determined by the Kaplan–Meier method. These findings suggest the importance of a long-time follow-up of IgAN even in mild cases.

In our study, it was difficult to compare the natural course of IgAN between cohorts due to differences in multiple factors, including patient biological differences, nephrologists' practice patterns (e.g. biopsy timing), and geography. Available data on the clinical course of patients with IgAN in the literature is variable [11–16]. Shen et al. reported that hematuria disappeared in 16 (12 %) of 135 IgAN patients presenting with isolated microscopic hematuria (mean observation period 92±28 months) and that hematuria, microalbuminuria, and tubulointerstitial lesions were useful markers for identifying patients at high risk for renal progression [17]. Gutierrez et al. observed remission in 37.6 % of 141 patients with IgAN who presented with microhematuria and proteinuria of <0.5 g/day at renal biopsy (59 patients treated with ACEI/ARB; mean observation period 108 months) and their multivariate analysis revealed that age and focal segmental glomerular sclerosis lesions in renal biopsy were significant risk factors for renal survival [18].

Our study is characterized by several limitations. First, the criteria used for prescribing medication after the diagnosis of IgAN by biopsy were not clear because of the
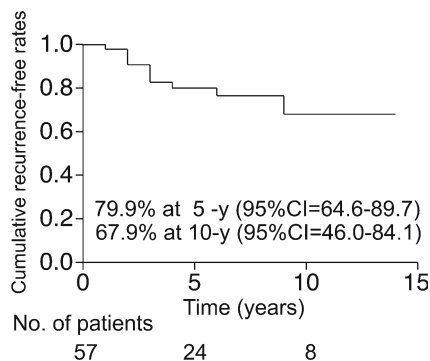

Fig. 3 Kaplan–Meier plot of the cumulative recurrence-free rates after spontaneous remission in children with IgAN showing minor glomerular abnormality or focal mesangial proliferation

79.9% at 5 -y (95%CI=64.6-89.7)
67.9% at 10-y (95%CI=46.0-84.1)

No. of patients
57   24   8

retrospective nature of this study. Second, there is the possibility of slight inconsistencies in the biopsy criteria used during the long study period, although the fundamental renal biopsy criteria were not changed during the entire study period.

In conclusion, our study clarified the occurrence of spontaneous remission in IgAN. In present-day Japan, although almost all pediatric patients with IgAN showing proteinuria seem to receive medication, physicians should consider the potential for spontaneous remission and refrain from aggressive treatment in those patients with mild IgAN.

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