Fukushima J. Med. Sci.,
Vol. 69, No. 2, 2023

[Original articles]

Differences in response to treatment in children with severe IgA nephropathy according to patient age

Yukihiko Kawasaki[1)2)], Yohei Kume[2)], Atsushi Ono[2)], Ryo Maeda[2)] and Hayato Go[2)]

[1)]Fukushima Medical University, Regional Medical Support Center, [2)]Department of Pediatrics, Fukushima Medical University School of Medicine, Fukushima, Japan

(Received November 24, 2022, accepted March 30, 2023)

Abstract

Aim : To clarify whether the response to treatment of IgA nephropathy (IgAN) differs depending on patient age, we examined the response to treatment according to age of onset in children with IgAN. *Methods* : We collected data for 44 children with severe IgAN. The children were retrospectively divided into three groups based on their age at disease onset. Group 1 consisted of 24 children under 11 years old, group 2 consisted of 9 children aged 12 to 13 years, and group 3 consisted of 11 children aged over 14 years old. The clinical features and prognosis were analyzed for each group. *Results* : The urinary protein excretion and serum IgA values in group 3 were higher than those in groups 1 and 2 at the most recent follow up, and histological findings showed that the MESTCG scores in group 3 were higher than those in group 1. Furthermore, the incidence of patients with persistent nephropathy or renal insufficiency in group 3 was higher than those in groups 1 and 2. *Conclusions* : Patients aged 14 years and older with IgAN may respond poorly to treatment compared with those younger than 14 years old. Therefore, care must be taken regarding response to treatment and relapse when treating older children.

Key words : age, IgA nephropathy, multi-drug combination therapy, Mizoribine, children

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis in the world at present. Pediatric IgAN in Japan has an average age of onset between 11 to 12 years and most are picked up from urinalysis performed at school. It was initially considered a benign disease with a favorable prognosis, but more recent data from long-term follow-up studies reveals that the disease progresses to renal failure in 2 to 10 % of pediatric patients and in 20 to 30% of adult patients[1-10)]. Clinical predictors of a poor outcome in patients with IgAN include age, renal insufficiency, heavier degrees of proteinuria, and hypertension, while pathologic features of a poor prognosis include glomerulosclerosis, interstitial fibrosis and tubular atrophy[2,5,6)]. Nozawa *et al.* showed that the age of onset and tubulointerstitial lesions were strong predictors of a progressive course in pediatric patients with IgAN[6)]. Further, Ikezumi *et al.* reported that pediatric IgAN manifests with proliferative glomerular lesions while, adults exhibit mesangial matrix expansion and interstitial fibrosis, and found that alternative activated M2 macrophages are present in areas of fibrosis containing myofibroblasts in adults, suggesting that they promote the development of fibrotic lesions[11)]. As age is cited as a factor related to poor prognosis for IgAN in adults and children, we hypothesized that the response to treatment of pediatric IgAN may differ depending on the age of onset.

To date, there have been few reports on age-related response to treatment in childhood acquired IgAN. In order to clarify whether the response to treatment of IgAN differs depending on age, we examined the response to treatment and prognosis ac-

Corresponding author : Yukihiko Kawasaki E-mail : kyuki@fmu.ac.jp

cording to the age of onset of the disease in children with severe IgAN.

Methods

The study was carried out under the auspices of the Committee for Human Experiments at Fukushima Medical University (Institutional Review Board Approval No. 2021-232). Informed consent was obtained from all patients or their parents.

Patients

We collected data for 44 children who had been diagnosed with IgAN with diffuse mesangial proliferation in the Department of Pediatrics, Fukushima Medical University School of Medicine, from January 1998 to December 2008, who had been treated with multi-drug combination therapy. The children were retrospectively divided into three groups based on the age of onset of IgAN. Group 1 consisted of 24 children under 11 years old, group 2 consisted of 9 children aged 12 to 13 years, and group 3 consisted of 11 children over 14 years old. The clinical features, laboratory and pathological findings at the first and second renal biopsies, and prognosis at the latest follow-up were analyzed for the three groups.

Definitions

Hematuria was defined as five or more red blood cells per high-power microscopic field in a centrifuged specimen. Patients were tested for proteinuria by quantitative determination of protein in 24-h urine specimens. "Diffuse mesangial proliferation" was defined on the basis of the World Health Organization criteria as 80% or more of the glomeruli showing moderate or severe mesangial cell proliferation, i.e., three or more mesangial cells per peripheral mesangial area. The estimated glomerular filtration rate (eGFR) was calculated based on the serum creatinine level and patient height[12].

The clinical status of each patient was classified into one of the following stages :

Stage 0 : Normal. The results of the physical examination were normal, and the patient had normal urine and normal renal function.

Stage 1 : Minor urinary abnormalities. The results of the physical examination were normal, but the urinalysis revealed microscopic hematuria or proteinuria of less than 20 mg/m^2/h.

Stage 2 : Persistent nephropathy. The patient had proteinuria of 20 mg/m^2/h or more and the eGFR was 60 ml/min/1.73 m^2 or greater.

Stage 3 : Renal insufficiency. The patient had an eGFR value less than 60 ml/min/1.73 m^2.

Pathology

The first renal biopsy was performed before treatment in all 44 children, while the second renal biopsy was performed during the recovery phase in all patients (24.8 ± 2.4 months after the initiation of treatment). For this study, we selected the four pathology variables proposed in the Oxford classification : namely, mesangial hypercellularity, segmental glomerulosclerosis or adhesion, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis as well as crescents and global glomerulosclerosis[13]. The immunofluorescence (IF) staining results for IgG, IgA, IgM, C1q, C3, C4 and fibrinogen were then examined.

Therapeutic interventions

Treatment of pediatric IgAN in Japan is based on the IgAN treatment guidelines and the IgAN clinical practice guidelines. In both cases, the treatment of pediatric IgAN in Japan is classified into 'mild cases' and 'severe cases' on the basis of clinical or histological severity[14-16]. In mild cases, 'clinical findings' consist of slight proteinuria (an early morning urine protein-to-creatinine ratio <1.0) and normal renal function (eGFR 90 ml/min/1.73 m^2 or more), and 'histological findings' consist of <80% of glomeruli showing moderate or severe mesangial proliferation, crescent formation, adhesions, or sclerosis and <30% of glomeruli showing crescent formation. In severe cases, 'clinical findings' consist of heavy proteinuria (an early morning urine protein-to-creatinine ratio >1.0) or renal dysfunction (eGFR 90 ml/min/1.73 m^2 or less) and 'histological findings' consist of >80% of glomeruli showing moderate or severe mesangial proliferation, crescent formation, adhesions, or sclerosis or >30% of glomeruli showing crescent formation.

The clinical practice guidelines recommend the use of angiotensin-converting enzyme (ACE) inhibitors, ACEI (lisinopril 0.4 mg / kg / day, maximum 20 mg / day) as a single agent for the treatment of mild IgAN. For severe IgAN, the Pediatric IgAN Treatment Guideline 1st Edition recommends 2-year multidrug therapy with prednisolone, immunosuppressive agents such as mizoribine (MZB) and azathioprine (AZP), anticoagulants, and antiplatelet drugs[15].

For this reason, we treated the patients with IgAN by dividing them into mild and severe types. The patients with mild IgAN were treated with ACEI, and the patients with severe IgAN were

treated with multi-drugs combination therapy such as prednisolone, MZB, warfarin and dilazep dihydrochloride. Prednisolone was given orally at a dose of 2 mg/kg/day in 3 divided doses for a total dose of not more than 60 mg/day for 2 weeks, followed by 1.5 mg/kg/day for 2 weeks, 1.0 mg/kg/day for 4 weeks, 0.5 mg/kg/day for 4 weeks, 1.0 mg/kg/2 days for 9 months, and 0.5 mg/kg/2 days for 12 months. MZB was given orally at a dose of 5 mg/kg/day in 2 divided doses for 24 months. Warfarin was given orally at a dose of 1-2 mg/day. Dilazep dihydrochloride was given orally at a dose of 5 mg/kg/day in 3 divided doses for 24 months.

Statistics

Data are expressed as the mean values ± SD. The statistical analysis was performed using a software package for statistical analysis (Version 4 of Stat View, Abacus Concepts, Berkeley, Calif., USA). Differences in the laboratory findings between the two groups were assessed using the Mann-Whitney rank sum test or contingency tables (chi square test).

Results

1) Comparison of baseline characteristics between the three groups

The age of onset and duration of follow-up from the initial therapy were 9.0 ± 2.0 and 8.6 ± 2.2 years, respectively, in group 1, 12.4 ± 0.4 and 9.1 ± 1.7 years in group 2 and 14.7 ± 0.4 and 9.3 ± 1.7 years in group 3. The male-to-female ratios were 17 : 7 and 3 : 6 and 8 : 3 in group 1, group 2 and group 3, respectively. Duration from onset to renal biopsy and duration from the first renal biopsy to the second biopsy were 4.4 ± 3.7 and 24.9 ± 2.5 months, respectively, in group 1, 6.7 ± 4.7 and 23.9 ± 2.8 months in group 2, and 4.9 ± 3.9 and 25.8 ± 2.0 months in group 3 (Table 1).

2) Comparison of laboratory findings at the time of the first and second renal biopsies, and at the most recent follow up between the three groups

At the time of the first renal biopsy, the serum IgA value in group 3 was higher than that of group 1, while the eGFR values did not differ between the three groups (Figure 1). At the time of the second renal biopsy and at the most recent follow up, the serum IgA value in group 3 was higher than those of groups 1 and 2, while the eGFR value in group 3 was lower than those of groups 1 and 2.

At the most recent follow up, the urinary protein excretion, incidences of hematuria, and serum IgA values in group 3 were higher than those of group 1 and group 2. The eGFR value in group 3 was lower than those of groups 1 and 2.

With regard to the serum IgA values, the serum IgA values of group 1 and group 2 at the time of the second renal biopsy were lower than those at the time of the first renal biopsy ($p<0.05$, $p<0.05$, respectively) and the serum IgA values in group 3 did not differ between the first and second renal biopsy. The serum IgA values in group 1 and group 2 at the most recent follow up were lower than those at the time of the first biopsy, and the serum IgA values in group 3 did not differ between the values from the most recent follow up and the first biopsy.

3) Comparison of the pathological findings at the first and second renal biopsy between the three groups

The IF findings revealed that amounts of IgA, C3 and fibrinogen in the glomeruli at the time of the second renal biopsy were lower than those at the time of the first renal biopsy ($p<005$) in each group. At the time of the first renal biopsy, the amount of glomerular C3 in group 3 was higher than that in group 2 ($p<0.05$), and at the time of the second renal biopsy, the amount of glomerular C3 in group 3 was higher than that in group 2 ($p<0.05$) (Table 2).

Table 1. Comparison of clinical manifestations between the three groups

	Group 1 ($n=24$)	Group 2 ($n=9$)	Group 3 ($n=11$)
Age at onset (years)	9.0±2.0	12.4±0.4	14.7±0.4
Duration from onset of symptoms to biopsy(months)	4.4±3.7	6.7±4.7	4.9±3.9
Gender(male : female)	17 : 07	3 : 06	8 : 03
Duration from onset to the latest follow-up period (years)	8.6±2.2	9.1±1.7	9.3±1.7
Time from first biopsy to second biopsy (years)	24.9±2.5	23.9±2.8	25.8±2.0
Mean blood pressure (mmHg)	80.8±8.3 a	85.2±10.1	88.1±8.6 a

a $p<0.01$, b $p<0.05$
The mean blood pressure in group 3 was higher than that in group 1.

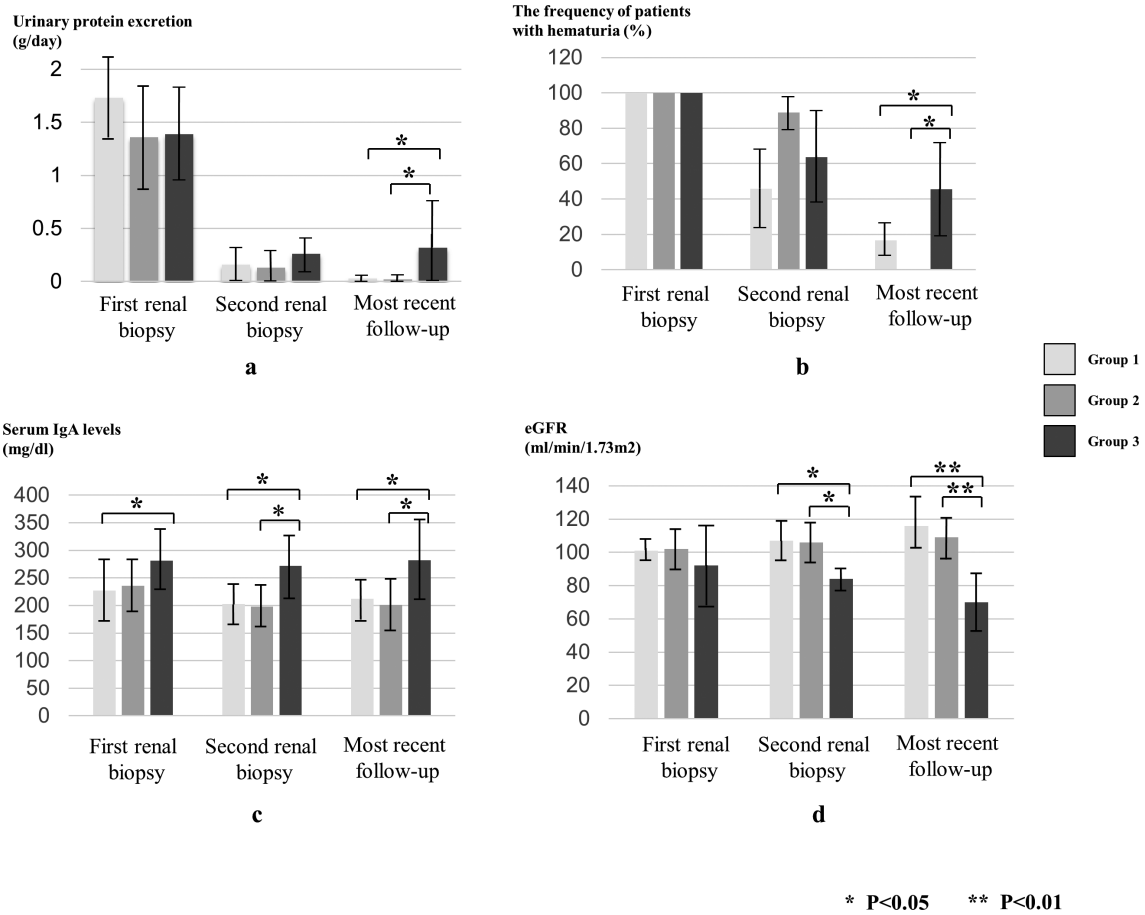

Fig. 1. Comparison of urinary protein excretion (a), frequency of patients with hematuria (b), serum IgA levels (c), and eGFR (d) between three patient groups at the time of first biopsy, second biopsy and at the most recent follow-up.

Table 2. Comparison of IF findings between the three groups

	First renal biopsy			Second renal biopsy		
	Group 1 (n=24)	Group 2 (n=9)	Group 3 (n=11)	Group 1 (n=24)	Group 2 (n=9)	Group 3 (n=11)
Glomerular IgA	2.54±0.55	2.27±0.44	2.64±0.45	2.00±0.63	1.89±0.45	2.14±0.78
Glomerular IgM	0.23±0.47	0.39±0.47	0.50±0.50	0.15±0.31	0.17±0.35	0.10±0.34
Glomerular IgG	0.46±0.72	0.78±0.80	0.41±0.49	0.42±0.78	0.17±0.50	0.36±0.55
Glomerular C1	0.13±0.37	0.06±0.17	0.0±0.0	0.04±0.14	0.00±0.00	0.05±0.15
Glomerular C3	1.23±0.88	1.17±0.76 a	1.50±0.50 a	0.79±1.13	0.67±0.51 b	1.14±0.90 b
Glomerular C4	0.02±0.00	0.02±0.00	0.02±0.00	0.04±0.20	0.00±0.00	0.00±0.00
Glomerular Fibrinogen	1.69±1.11	1.83±1.00	1.14±0.92	0.90±0.98	0.89±0.93	0.82±0.75

a, b $p<0.05$

At the time of the first renal biopsy, the amount of C3 in group 3 was higher than that in group 2 ($p<0.05$), and at the time of the second renal biopsy, the amount of C3 in group 3 was higher than that in group 2 ($p<0.05$).

Histological analyses according to the Oxford classification criteria showed the ratios of M0M1, E0E1, S0S1, T0T1T2, absence/presence of crescents and MESTCG scores at the time of the second biopsy were lower than those at the time of the first biopsy in each group. At the time of the second biopsy, MESTCG scores, the percentage of glomeruli showing crescents and glomerulosclerosis in group 3 were higher than those in group 1, but there were no significant differences in the ratios of M0M1, E0E1, S0S1, T0T1T2, absence/presence of crescents, global sclerosis, and MESTCG scores at the

Table 3. Comparison of pathological findings between the three groups

Pathology (Oxford criteria)	First renal biopsy			Second renal biopsy		
	Group 1 (n=24)	Group 2 (n=9)	Group 3 (n=11)	Group 1 (n=24)	Group 2 (n=9)	Group 3 (n=11)
Mesangial score (M0/M1)	0/24	0/9	0/11	12/12	4/5	5/6
Endocapillary hypercellularity (E0/E1)	7/17	2/7	0/11	24/0	4/5	5/6
Segmental sclerosis and adhesion (S0/S1)	0/24	0/9	1/10	1 7/7	6/3	5/6
Tubular atrophy and interstitial fibrosis (T0/T1/T2)	1/20/3	0/6/3	0/4/7	1 7/7/0	6/3/0	4/5/2
Crescent (absent/present)	1/23	0/9	0/11	22/2 a	8/1	7/4 a
Glomerular sclerosis (absent/present)	11/13	3/6	3/8	15/9 b	6/3	3/8 b
MESTCG scores	5.3±1.0 c	5.8±0.8	6.5±1.0 c	1.5±1.4 d	1.7±1.7	3.1±2.0 d
Crescent formation (%)	28.5±21.1	41.9±14.6	35.5±19.2	1.0±3.8	2.5±5.8	5.8±13.9

a,b,c,d $p<0.05$

At the time of the second biopsy, MESTCG scores, the percentage of glomeruli showing crescents and glomerulosclerosis in group 3 were higher than those in group 1.

time of the first and second biopsy between group 1 and group 2 (Table 3).

4) Comparison of clinical stage at the most recent follow-up and side effects between the three groups

At the most recent follow up, 23 patients (95.8%) in group 1, 9 (100%) in group 2, and 7 (63.6%) in group 3 had normal urine or minor urinary abnormalities, while one patient (4.2%) in group 1, none in group 2 and 4 (36.3%) in group 3 had persistent nephropathy or renal insufficiency. The incidence of patients with persistent nephropathy or renal insufficiency in group 3 was higher than those in group 1 and group 2 (Table 4).

Discussion

IgAN is particularly common in young adults, with progression toward end-stage kidney disease (ESKD) over 20 years in about one third of patients. The median age of patients starting dialysis ranges from 40 to 50 years of age. Generally, in children, more recent data from long-term follow-up studies revealed that the disease progressed to renal failure in 2 to 10 % of patients, with pediatric IgAN considered to have a better prognosis than IgAN in adults. Previously, we also showed that pediatric IgAN has a benign course and the risk for end-stage renal disease is lower than that in adults. On the other hand, it was clarified that the age of onset and the degree of interstitial dysfunction are predictive prognostic factors for IgAN in children[6]. However, there are no reports on the response to treatment or prognosis of pediatric IgAN according to age when undergoing similar treatment. Thus, we investigated the response to treatment according to age of onset in children with severe IgAN undergoing multi-drug combination therapy. The average age of onset of pediatric IgAN is 11 to 11.6 years old, and puberty starts at 11 years old. Thus, we divided the patients into before puberty (group 1 : 11 years and younger), early adolescence (group 2 : 11-14 years), and mid-puberty (group 3 : 14 years and older). Our study revealed that response to treatment differed between patients under 14 years old and patients over 14 years old (i.e., groups 1 and 2 vs. group 3), and the proportion of patients with renal insufficiency and high serum IgA values at the time

Table 4. Comparison of prognosis between the three groups

Stage	First renal biopsy			Second renal biopsy		
	Group1 (n=24)	Group 2 (n=9)	Group 3 (n=11)	Group 1 (n=24)	Group 2 (n=9)	Group 3 (n=11)
Stage 1	0 (0%)	0 (0%)	0 (0%)	20 (83.3%)	6 (66.7%)	4 (36.4%)
Stage 2	0 (0%)	0 (0%)	0 (0%)	3 (12.5%)	3 (33.3%)	3 (27.3%)
Stage 3	24 (100%)	8 (88.9%)	11 (100%)	1 (4.2%)	0 (0%)	3 (27.3%)
Stage 4	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	1 (9.0%)

The incidence of patients with persistent nephropathy or renal insufficiency in group 3 was higher than those in group 1 and group 2 ($p<0.05$).

of the latest observation in children over 14 years old with IgAN were higher than that of children under 14 years old with IgAN. Thus, our results showed that the response to treatment in children with IgAN varies with age.

Based on an evaluation of the characteristics of IgAN in children and adults, Selewski found better long-term outcomes in patients diagnosed with IgAN as children or adolescents than in those diagnosed as adults, and our results are consistent with those findings[14]. Furthermore, when considering only patients with focal or diffuse proliferative IgAN lesions, Haas *et al.* found that patients diagnosed as children or adolescents had a 10-year actuarial renal survival of 80%, compared to 35% in patients diagnosed as adults, while in patients with diffuse proliferative glomerulonephritis, the 10-year renal survival of patients diagnosed before age 18 was 63%, compared with 0% in those diagnosed as adults[15]. Patients with IgAN diagnosed as adults tend to have more advanced lesions, as manifested by more frequent and severe renal insufficiency, a greater incidence of hypertension and more chronic morphologic changes[11,17-19]. In addition, Cambier *et al.* showed that a higher proportion of glomerular inflammation with mesangial and endocapillary hypercellularity in children than adults, while chronic lesions with focal glomerulosclerosis/adhesion, tubular atrophy/interstitial fibrosis ≥ 25% and podocytopathic features (which may be responsive to steroids) were higher in adults than in children[19].

Although the above differences were observed between pediatric and adult patients with IgAN, we investigated whether there are differences in response to treatment and prognosis due to age differences among the childhood age groups.

With regard to the laboratory findings and clinical course, there were no age-related effects observed for urinary protein excretion, frequency of patients with hematuria, or eGFR at the first biopsy, but the serum IgA level was significantly higher in the patients over 14 years old. At the time of the second renal biopsy after multi-drug combination therapy, urinary protein excretion showed a significant reduction in each group, and there was no difference between age groups in urinary protein excretion or the frequency of patients with hematuria. However, the eGFR level was significantly reduced in the patients over 14 years old. Furthermore, at the most recent follow-up, an increase in urinary protein excretion was observed only in the patients over 14 years old. With regard to the presence of hematuria, improvement was seen in the patients under 14 years old, but the residual rate of hematuria was high and the eGFR level decreased in the patients over 14 years old.

In terms of the pathological findings, the ratios of M0M1, E0E1, S0S1, T0T1T2, absence/presence of crescents and MESTCG scores at the time of the second renal biopsy were lower than those at the time of the first biopsy in each age group, indicating that histological improvements had occurred. In addition, although there was no difference in the degree of tissue damage according to age at the time of the first biopsy, the histological findings at the time of the second renal biopsy showed that the MESTCG score, percentage of glomeruli showing crescents and glomerulosclerosis in the patients over 14 years old were higher than those of the patients under 14 years old. The second renal biopsy in the patients over 14 years old revealed a high rate of active lesions and sclerosing lesions compared with the rate found in the patients under 14 years old.

At the most recent follow up, 32 of 33 patients aged under 14 years and 7 of 11 patients aged over 14 years showed normal urinary findings or mild urinary abnormalities, while one of the 33 patients aged under 14 years and 4 of the 11 patients aged over 14 years showed persistent nephropathy or renal insufficiency. In the patients aged over 14 years, the rate of persistent nephropathy or renal insufficiency was high, and there were some cases with relapse after multi-drugs combination therapy. In our study, even with IgAN treatment, if the age of onset is over 14 years old and the patient presents with diffuse mesangial proliferation, it is necessary to pay attention to a poor response to treatment and relapse after treatment.

Ronkainen *et al.* evaluated the natural long-term outcome after pediatric IgAN[20]. Altogether 55 patients with biopsy-proven IgAN were identified, only 37 (67%) responded to the health questionnaire and 31 (56%) participated in the medical examination after a mean follow-up of 18.7 years (SD 6.2 ; range 8.5-29.8). They found poorer outcomes for children or adolescents diagnosed with IgAN at an older age as compared with those diagnosed at a younger age.

At present, it is unclear as to why the response to treatment differs between adult and pediatric patients with IgAN. Although the reason is not clear from our research, we speculate that the following factors are important. 1) Compared to groups 1 and 2, group 3 tended to have more patients with high serum IgA levels at the time of initial renal biopsy, patients with strong glomerular C3 deposition on IF,

and patients with high MESTCG score and high crescent formation rate even on light microscopy. Therefore, it is possible that patients in group 3 had stronger IgA production ability, including aberrantly glycosylated IgA, compared to the patients in other groups before treatment. 2) Furthermore, at the time of the second renal biopsy, group 3 had higher serum IgA levels, stronger glomerular C3 deposition on IF, and more severe renal tissue damage compared to patients in groups 1 and 2.

In patients in group 3, it is possible that the production of aberrantly glycosylated IgA could not be suppressed even by combination therapy with immunity and inflammation suppression.

Limitations

The present study was relatively small in scale, and we are now attempting to confirm the above findings in a large-scale study examining differences in response to treatment according to age in children with IgAN with diffuse mesangial proliferation. Furthermore, in order to show that the age of onset is related to renal prognosis and treatment response, it is not sufficient to simply compare changes in urinary protein and eGFR in each group. After setting the outcome based on urinary protein responsiveness such as remission and incomplete remission, survival analyzes and adjustments for baseline covariates should be performed to demonstrate that age of onset is a significant risk for outcomes. Additionally, there are differences in the duration of follow-up and blood pressure between groups in our study, which may affect the results.

Conclusions

Pediatric IgAN may show differences in response to treatment and prognosis in patients over 14 years old, and care must be taken regarding response to treatment and relapse when treating older children.

Compliance with ethical standards

Conflict of interest

No authors have any conflicts of interest or financial support related to the present study.

The study was carried out under the auspices of the Committee for Human Experiments at Fukushima Medical University (Institutional Review Board Approval No 2021-232).

Informed consent

Informed consent was obtained from all patients or their parents.

References

1. Berger J, Hinglais N. Les depots intercapillaireis d'IgA-IgG. J Urol Nephrol, **74** : 694-695, 1968.
2. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med, **368** : 2402-2414, 2013.
3. Andreoli SP, Bergstein JM : Treatment of severe IgA nephropathy in children. Pediatr Nephrol, **3** : 248-253, 1989.
4. Suzuki H, Kiryluk K, Novak J, *et al.* The pathophysiology of IgA nephropathy. J Am Soc Nephrol, **22** : 1795-1803, 2011.
5. Kusumoto Y, Takebayashi S, Taguchi T, Harada T, Naito S : Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and in adult Japanese. Clin Nephrol, **28** : 118-124,1987.
6. Nozawa R, Suzuki J, Isome M, Kawasaki Y, Suzuki S, Suzuki H. Clinicopathological features and the prognosis of IgA nephropathy in Japanese children on long-term observation. Clin Nephrol, **64** : 171-179, 2005.
7. Yoshikawa N, Ito H, Sakai T, *et al.* A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. J Am Soc Nephrol, **10** : 101-109, 1999.
8. Kawasaki Y, Suzuki J, Sakai N, *et al.* Efficacy of prednisolone and mizoribine therapy for disuse IgA nephropathy. Am J Nephrol, **24** : 147-153, 2004.
9. Kamei K, Nakanishi K, Ito S, *et al.* Long-term results of a randomized controlled trial in childhood IgA nephropathy. Clin J Am Soc Nephrol, **6** : 1301-1307, 2011.
10. Kawasaki Y, Suyama K, Miyazaki K, *et al.* Resistance factors for the treatment of immunoglobulin A nephropathy with diffuse mesangial proliferation. Nephrology (Carlton), **19** : 384-391, 2014.
11. Ikezumi Y, Suzuki T, Karasawa T, *et al.* Identification of alternatively activated macrophages in new-onset paediatric and adult immunoglobulin A nephropathy : potential role in mesangial matrix expansion. Histopathology, **58** : 198-210, 2011.
12. Uemura O, Honda M, Matsuyama T, *et al.* Is the new Schwartz equation derived from serum creatinine and body length suitable for evaluation of renal function in Japanese children? Eur J Pediatr, **171** : 1401-1404, 2012.
13. Working Group of the International IgA Nephropathy Network, the Renal Pathology Society, Coppo R, Troyanov S, *et al.* The Oxford IgA nephropathy clinicopathological classification is valid for chil-

dren as well as adults. Kidney Int, **77** : 921–927, 2010.
14. Nakanishi K, Yoshikawa N. Immunoglobulin A Nephropathy. Section5. Glomerular Disease. In : Avner ED, Harmon WE, Niaudet P, Yoshikawa N (d) Pediatric Nephrology Vol 2 6thEd. Springer 757–782, 2009.
15. Clinical Practice Guidelines for Pediatric IgA Nephropathy 2020 Japan Society for Pediatric Nephropathy / Editing Diagnosis and Treatment https://minds.jcqhc.or.jp/docs/gl_pdf/G0001187/4/iga_nephropathy_in_children.pdf Shindantotiryosya in Japanese
16. Suzuki H, Kikuchi M, Koike K, *et al.* A digest from evidence-based clinical practice guideline for IgA nephropathy 2020. Clin Exp Nephrol, **25** : 1269–1276, 2021.
17. Selewski DT, Ambruzs JM, Appel GB, *et al.* Clinical Characteristics and Treatment Patterns of Children and Adults with IgA Nephropathy or IgA Vasculitis : Findings From the CureGN Study. Kidney Int Rep, **3** : 1373–1384, 2018.
18. Haas M, Rahman MH, Cohn RA, Fathallah-Shaykh S, Ansari A, Bartosh SM. IgA nephropathy in children and adults : comparison of histologic features and clinical outcomes. Nephrol Dial Transplant, **23** : 2537–2545, 2008.
19. Cambier A, Rabant M, El Karoui K, *et al.* Clinical and histological differences between adults and children in new onset IgA nephropathy. Pediatr Nephrol, **35** : 1897–1905, 2020.
20. Ronkainen J, Ala-Houhala M, Autio-Harmainen H, *et al.* Long-term outcome 19 years after childhood IgA nephritis : a retrospective cohort study. Pediatr Nephrol, **21** : 1266–1273, 2006.