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IgA Nephropathy in Children: A Multicenter Study in Poland

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Abstract

IgA nephropathy (IgAN) is the most common form of glomerulonephritis in pediatric population. The clinical presentation of the disease in children ranges from microscopic hematuria to end-stage kidney disease. The aim of the study was to retrospectively assess clinical and kidney biopsy features in children with IgAN. We assessed a cohort of 140 children, 88 boys, 52 girls with the diagnosis of IgAN in the period of 2000–2015, entered into the national Polish pediatric IgAN registry. The assessment

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included the following: proteinuria, hematuria, glomerular filtration rate (GFR), arterial blood pressure, and the renal pathological changes according to the Oxford classification and crescents formation, as modifiable and unmodifiable risk factors. The incidence of IgAN in Poland was set at 9.3 new cases *per* year. The mean age at onset of IgAN was 11.9 ± 4.3 years, and the most common presentation of the disease was the nephritic syndrome, recognized in 52 % of patients. Kidney biopsy was performed, on average, 1.3 ± 2.0 years after onset of disease. Based on the ROC analysis, a cut-off age at onset of disease for GFR <90 mL/min/1.73 m^2 (risk factor of progression) was calculated as 13.9 years. Unmodifiable lesions: segmental sclerosis, tubular atrophy/interstitial fibrosis (S1, T1-2) in the Oxford classification and crescents in kidney biopsy were significantly more common in Gr 1 (>13.9 years) compared with Gr 2 (<13.9 years), despite a significantly shorter time to kidney biopsy in the former. We conclude that IgAN in children may be an insidious disease. A regular urine analysis, especially after respiratory tract infections, seems the best way for an early detection of the disease.

Keywords

Children • Glomerulonephritis • Hematuria • IgA nephropathy • IgA protein • Kidney • Proteinuria • Respiratory infection • ROC analysis

1 Introduction

IgA nephropathy (IgAN) is the most common type of chronic glomerulonephritis worldwide (Pesce et al. 2016; Wyatt and Julian 2013; McGrogan et al. 2011; Coppo and D'Amico 2005; D'Amico 1987). The incidence of this condition in children is estimated at 0.03/100,000/year in Venezuela, 0.5–1.0/100,000 children/year in the US, and 9.9/100,000 children/year in Asia (Shibano et al. 2015; Orta-Sibu et al. 2002; Wyatt et al. 1998). Based on the findings reported, a map of genetic susceptibility to IgAN worldwide has been created (Kiryluk et al. 2012). The disease is more common in boys and typically manifests with episodic hematuria occurring in the course or after an upper respiratory tract infection (Wang et al. 2012; Schena 1990).

The pathogenesis of IgAN is not entirely clear, but recent studies favor a four-hit hypothesis (Suzuki et al. 2011). A key pathogenetic role is played by galactose deficiency in the hinge region of the IgA1 molecule (Hit 1), produced in response to infections, mostly of the upper airways (Mestecky et al. 2005). This results in the formation of an aberrant galactose-deficient IgA1 (GdIgA1). Then, GdIgA1 induces the formation of IgG or IgA1 antibodies (Hit 2). These antibodies recognize GalNAc-containing epitopes in the hinge region O-glycans of GdIgA1 (Tomana et al. 1999). The presence of GdIgA1 and anti-GdIgA1 antibodies in the serum leads to the formation of pathogenic IgA1 that contain immune complexes (Hit 3). In patients with IgAN and Henoch-Schönlein nephritis (HSN), a large size of IgG-IgA1 immune complexes does not allow their hepatic degradation *via* the asialoglycoprotein receptor (ASGPR), resulting in their entry to the renal circulation. Mesangial localization of immune complexes induces an autoimmune inflammatory

response, proliferation of mesangial cells, and expression of extracellular matrix components (Hit 4), leading to glomerular and interstitial damage and frequently to renal failure (Suzuki et al. 2011). The inflammatory process in the glomerular structure is associated with inflammation in the tubulointerstitium and infiltration by immune cells of variable intensity (Gluhovschi et al. 2009). The diagnosis can be made only on the basis of kidney biopsy which unravels IgA deposits by immunofluorescence staining (Berger and Hinglais 1968).

Previous histopathologic classifications of IgAN included various elements of biopsy findings. The Oxford classification introduced in 2009 includes four adverse prognostic components: mesangial proliferation (M), endocapillary hypercellularity (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T) (Coppo et al. 2014; Cattran et al. 2009). In recent years, a distinction between modifiable (M, E, and crescents) and unmodifiable (S and T) changes has been added to the classification (Coppo and Davin 2015). In Japan, a school urine screening program has been functioning since 1974. It enables early diagnosis and treatment of glomerulopathy, resulting in a decreasing rate of end-stage renal failure secondary to glomerulonephritis (Shibano et al. 2015).

The clinical course of IgAN is milder in children (Nozawa et al. 2005; Haas 1997). However, the age at onset can be an independent predictor of poor outcome and renal failure (Radford et al. 1997). A pediatric registry of IgAN has been established in Poland in 2013. The present study was undertaken to analyze epidemiological, clinical, and histopatological data of IgAN children, retrieved from this registry.

2 Methods

The Research Review Board of Warsaw Medical University in Poland approved this study. The consent requirement was waived because of the retrospective nature of the analysis of medical records. We retrospectively examined records of 140 children, including 88 boys and 52 girls, (mean age of 11.4 $\pm$ 4.3 years) with the diagnosis of IgAN, based on the presence of IgA as the predominant immunoglobulin in the glomerular mesangium according to the Oxford classification. The patients from nine pediatric nephrology units in Poland were entered into the registry in the years 2000–2015.

In all patients, demographic data, symptoms at disease onset, including proteinuria, microscopic hematuria, hypertension, glomerular filtration rate (GFR), history of a preceding infection, family history of glomerulopathy, and kidney biopsy findings were analyzed. Proteinuria was determined using the Exton method and expressed in mg/kg/day. Nephrotic range proteinuria was defined as $\geq$50 mg/kg/day, and nephritic (non-nephrotic) range proteinuria was defined as $<$50 mg/kg/day. Nephritic syndrome was defined as microscopic hematuria combined with nephritic (non-nephrotic) range proteinuria. Microscopic hematuria was defined as the presence of $>$5 erythrocytes in the urine sediment *per* viewfield in light microscopy at 400-fold magnification, and gross hematuria was diagnosed when a change in urine color was present. Isolated microscopic/gross hematuria was recognized when it was unaccompanied by other abnormalities in urinalysis. Hypertension was diagnosed when blood pressure on three occasions was above the 95th percentile for height, age, and gender (National High Blood Pressure Education Program 2005). Glomerular filtration rate was calculated using the Schwartz formula (eGFR = 0.413 x height/serum creatinine) (Schwartz et al. 2009). A positive history of a preceding infection was defined as an infection within 3 weeks before the development of IgAN symptoms. A positive family history of glomerulopathy was based on the kidney biopsy results in a family member.

Diagnostic kidney biopsy findings were evaluated in the participating units and further confirmed by a reference center, the Department of Pathology of Warsaw Medical University in Poland. The diagnosis was made when immunofluorescence testing showed predominant IgA deposits. Kidney biopsies were also scored using the Oxford classification (Coppo et al. 2014; Cattran et al. 2009), with the presence

of a given finding scored 1, and the absence scored 0. The following components were included: M – mesangial proliferation (M1 or M0); E – endocapillary hypercellularity (E1 or E0); S – segmental sclerosis/adhesions (S1 or S0); and T – tubular atrophy/interstitial fibrosis (T0 – 0–25 %, T1 – 26–50 %, and T2 > 50 %). The MEST score was calculated as the sum of M + E + S + T, ranging from 0 to 5. The M1 and E1 changes and crescents were considered modifiable (active), and S1 and T1-T2 changes were considered unmodifiable (chronic).

Based on the severity of baseline proteinuria, which is an adverse prognostic, patients were categorized as having nephrotic range proteinuria (Group A), non-nephrotic range proteinuria (Group B), or isolated hematuria (Group C). We also analyzed patients in relation to the age at onset of disease.

2.1 Statistical Elaboration

Data were shown as means ± SD for normally distributed variables, and medians and ranges for non-normally distributed variables. Normality of distribution of variables was verified using the Lilliefors test. The Student *t*-test for independent samples was used to compare the mean values of normally distributed continuous variables between two groups, and the Mann-Whitney *U* test was used for non-normally distributed variables. Three-group comparisons were performed using univariate ANOVA and the Kruskal-Wallis test for normally and non-normally distributed variables, respectively.

Categorical variable frequencies in 2 or 3 groups were compared using the chi-squared test. The receiver operating characteristic (ROC) curve was used to determine a cut-off age optimal for dichotomization between normal and reduced GFR, i.e., for two-class categorization of GFR values ≥90 *vs.* <90 mL/min/1.73 m^2. The area under the curve (AUC) was considered statistically significant when greater than >0.5 at $p < 0.05$. A p-value <0.05 defined statistically significant differences.

Table 1 Demographic, clinical, and histopathologic characteristics of pediatric patients

	All (n = 140)
Male (n%)	88 (63 %)
Female (n%)	52 (37 %)
Age at onset (yr)	11.4 ± 4.3
Proteinuria (mg/kg/day)	
Mean	38.4 ± 99.0
Median (range)	13.0 (0–967)
GFR (mL/min/1.73 m^2)	94.2 ± 36.2
Time to biopsy (yr)	1.3 ± 2.0
MEST score	1.5 ± 1.1
M 1, n (%)	109 (78)
E 1, n (%)	30 (21)
S 1, n (%)	40 (29)
T 1–2, n (%)	24 (17)
Active lesions only	
M1/E1, n (%)	65 (46)
Chronic lesions	
S1/T1, n (%)	50 (36)

3 Results

Demographic, biochemical, and histological characteristics of the cohort studied are shown in Table 1. Based on the registry data, the incidence of IgAN in children was 9.3/100,000 *per* year, with the male to female ratio of 1.7:1, and the mean age at onset of disease of 11.4 ± 4.3 years. The mean baseline proteinuria was 38.4 ± 99.0 (median 13.0) mg/kg/day, and the mean GFR was 94.2 ± 36.2 mL/min/1.73 m^2.

The frequency of clinical manifestations of IgAN in children is shown in Table 2. The most common initial manifestation was nephritic syndrome with microhematuria, present in 50 % of patients, followed by isolated hematuria in 29 % of patients, and nephrotic range proteinuria with hematuria in 21 % of patients. Hypertension, as one of the initial manifestations of IgAN, was present in 17 % of patients, accompanying nephritic syndrome in 11 % of patients, nephrotic syndrome in 5 % of patients, and isolated microscopic/gross hematuria in 1 % of patients. GFR reduced below 90 mL/min was seen in 39 % children, including 23 % with nephritic syndrome, 10 % with nephrotic

Table 2 Clinical characteristics of pediatric patients with IgA nephropathy (IgAN)

Symptoms at onset of IgAN	n (%)	HTN	↓GFR	Gross hematuria	Previous infection	Family history of GN
Nephrotic proteinuria + hematuria	29 (21 %)	7 (5 %)	14 (10 %)	8 (6 %)	17 (12 %)	3 (2 %)
Nephritic proteinuria + hematuria	70 (50 %)	15 (11 %)	33 (23 %)	22 (16 %)	39 (28 %)	1 (1 %)
Isolated hematuria/gross hematuria	41 (29 %)	2 (1 %)	8 (6 %)	10 (7 %)	29 (21 %)	4 (3 %)
Overall	140 (100 %)	24 (17 %)	55 (39 %)	40 (29 %)	85 (61 %)	8 (6 %)

IgAN IgA nephropathy, *HTN* hypertension, *GRF* glomerular filtration rate, *GN* glomerulopathy

Table 3 Characteristics of pediatric patients in relation to the severity of proteinuria

	Group A Nephrotic proteinuria (n = 29)	Group B Non-nephrotic proteinuria (n = 70)	Group C Isolated hematuria (n = 41)	p
Age at onset (yr)	10.2 ± 4.7	12.1 ± 4.2	11.2 ± 4.3	0.09
Proteinuria – median (range) (mg/kg/day)	100 (50–967)	14.1 (4–50)	0	
GFR (mL/min/1.73 m^2)	90.3 ± 41.4	86.2 ± 34.2	110.9 ± 31.5	$<0.05^1$
GFR <90 mL/min/ 1.73 m^2; n (%)	14 (40)	33 (47)	8 (19)	$<0.05^2$
Infection at onset; n (%)	17 (59)	39 (56)	29 (70)	ns
Time to biopsy (yr)	0.7 ± 1.1	2.8 ± 10.8	1.6 ± 1.7	$<0.05^3$
MEST score	1.9 ± 1.2	1.6 ± 1.1	1.3 ± 0.8	$<0.05^4$
Active lesions M1/E1; n (%)	10 (34)	33 (47)	22 (54)	ns
Chronic lesions S1/T1; n (%)	11 (38)	30 (43)	9 (22)	$<0.05^5$

Significant differences: [1]A *vs.* C, B *vs.* C, [2]A *vs.* C, B vs C, [3]A *vs.* C, B *vs.* C; [4]A *vs.* C, [5]B *vs.* C

syndrome, and 6 % with isolated hematuria. GFR below 60 mL/min was noted at baseline in 16 (11 %) patients. Episodic hematuria as an initial disease manifestation was seen in 29 % of patients, most commonly with nephritic syndrome (16 %). An infection, mostly involving airways, preceded disease symptoms in 54 % of patients, and a positive family history of glomerulopathy was noted in 6 % of patients.

Kidney biopsy was performed in all children at the mean of 1.3 ± 2.0 (median 0.5) years since the initial manifestation of the disease (Table 1). The most common indication for kidney biopsy was nephritic syndrome (52 %). The most frequent changes according to the Oxford classification were M1 (mesangial proliferation) noted in 109 (78 %) of patients, while chronic S1 and T1/T2 changes were noted in 29 % and 17 % of children, respectively. The most common MEST score was 1, found in 61 (45 %) of patients.

Isolated active M1 and/or E1 changes were found in 65 children (46 %), including 10 (15 %) with nephrotic range proteinuria, 33 (51 %) with non-nephrotic range proteinuria, and 22 (34 %) with isolated hematuria. Crescents were present in 33 (23 %) children, most frequently fibrocellular in 17 (51 %) and fibrous in 12 (36 %). Unmodifiable S1 and/or T1/T2 changes were found in 50 (36 %) patients, most commonly with non-nephrotic range proteinuria or isolated hematuria. We found a positive correlation between the MEST score and baseline proteinuria ($r = 0.20$, $p < 0.05$), and a negative correlation between the MEST score and GFR ($r = -0.27$, $p < 0.05$).

Table 3 shows the correlation between MEST and GFR *vs.* proteinuria/hematuria (Group A –

nephrotic range proteinuria, Group B – non-nephrotic range proteinuria, and Group C – isolated hematuria). The age of patients in Group A tended to be lower than that in Group B ($p = 0.09$), but it did not differ significantly in relation to Group C. The mean GFR values were significantly lower, and the number of children with GFR <90 mL/min/1.73 m^2 was significantly higher in Groups A and B compared with Group C. The time to kidney biopsy was longer in Groups B and C compared with Group A. The mean MEST score was the highest in Group A (1.9 ± 1.2), with a significant difference compared with Group C. There was an insignificant trend toward more frequent MEST scores of 1 and 2 in Groups B and C compared with Group A, and toward MEST scores of 3 and 4 in Group A. No significant differences in the rates of isolated active M1/E1 changes and the presence of crescents were found among Groups A, B, and C. Unmodifiable changes were most common in Group B (43 %), significantly more common compared with Group C (21 %) ($p < 0.05$) and Group A (38 %) ($p > 0.05$). A negative correlation between the age at onset of disease and GFR was found ($r = -0.24$, $p < 0.05$).

Based on the analysis of ROC curves, we determined the cut-off level of age at ≥13.9 years, associated with GFR <90 ml/min/1.73 m^2 at onset of disease in children with IgAN [(AUC = 0.62, sensitivity 0.768 (95 % CI 0.62–0.854), specificity 0.466 (95 % CI 0.33–0.601), $p < 0.05$)] as risk factor of poor prognosis (Fig. 1).

We also defined two age-groups: above (Group 1) or below (Group 2) the cut-off age level of 13.9 years, to compare laboratory and other findings as shown in Table 4. We failed to find any significant differences in the severity of baseline proteinuria, the presence of hematuria and hypertension, and the rate of preceding infections between the two age-groups, and between the subgroups A1/A2, B1/B2, and C1/C2 defined by the greater (A1, B1, and C1) or smaller (A2, B2, and C2) severity of baseline proteinuria.

Kidney biopsy was performed after a significantly shorter time from the initial disease symptoms in Group 1 (aged >13.9 years) compared with Group 2 (aged <13.9 years) ($p < 0.05$). The time from initial disease symptoms to kidney biopsy did not differ between subgroups A1 and A2, and between subgroups C1 and C2, but kidney biopsy was performed significantly earlier in subgroup B1 (age >13.9 years with non-nephrotic range proteinuria) compared with subgroup B2 (age

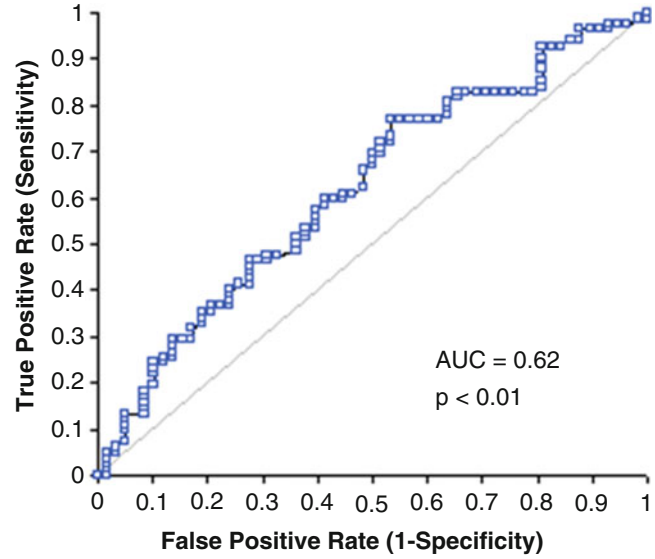

Fig. 1 Receiver operating characteristic (ROC) curve designating a cut-off level of age associated with glomerular filtration rate (GFR) < 90 ml/min/1.73 m^2 at onset of disease in children with IgA nephropathy (IgAN)

Table 4 Clinical and histopathological data of pediatric patients with IgA nephropathy (IgAN) in relation to age

	Overall (n = 140)			Nephrotic proteinuria (n = 29)			Non-nephrotic proteinuria (n = 70)			Isolated hematuria (n = 41)		
	Group 1 (n = 46)	Group 2 (n = 94)	p	Group A1 (n = 9)	Group A2 (n = 20)	p	Group B1 (n = 23)	Group B2 (n = 47)	p	Group C1 (n = 14)	Group C2 (n = 27)	p
Age at disease onset (yr)	16.1 ± 1.8	9.1 ± 3.2	<0.001	15.4 ± 1.2	7.3 ± 3.0	<0.001	16.4 ± 2.0	10.2 ± 3.1	<0.001	16.0 ± 1.8	8.8 ± 2.9	<0.001
Proteinuria (mg/kg/day)												
mean proteinuria	70.7	45.8	ns	245.0	116.4	ns	20.4	15.2	ns	0	0	ns
median (min-max)	18.0 (2.5-967)	20.0 (3.5-500)		133.0 (51–967)	73.5 (50–500)		14.5 (2.5-50)	14.1 (2.5-39)		0	0	
GFR <90 mL/min/1.73 m^2, n (%)	25 (54)	30 (32)	<0.05	7 (78)	7 (35)	<0.05	14 (60)	19 (40)	ns	4 (29)	4 (15)	ns
Gross hematuria, n (%)	12 (26)	28 (30)	<0.01	0	8 (40)	<0.01	9 (39)	13 (28)	ns	3 (21)	7 (26)	ns
Hypertension, n (%)	8 (17)	16 (17)	ns	3 (33)	4 (20)	ns	3 (13)	12 (25)	ns	2 (14)	0	<0.05
Previous infection, n (%)	23 (50)	62 (66)	ns	3 (33)	12 (60)	ns	13 (56)	32 (68)	ns	7 (50)	18 (67)	ns
Family history of glomerulonephritis, n (%)	1 (2)	7 (7)	ns	1 (11)	2 (10)	ns	0	1 (2)	ns	0	4 (15)	<0.05
Time to biopsy (yr)	0.7 ± 0.8	1.6 ± 2.3	<0.05	0.2 ± 0.2	0.9 ± 3.0	ns	0.7 ± 0.8	1.8 ± 2.7	<0.05	1.2 ± 0.9	1.8 ± 2.1	ns
Active lesions, n (%)	18 (39)	47 (50)	ns	1 (11)	9 (45)	<0.05	10 (43)	23 (50)	ns	7 (50)	15 (55)	ns
M1	13 (28)	42 (45)	=0.05	1 (11)	8 (40)	ns	6 (26)	20 (42)	ns	6 (43)	14 (52)	ns
E1	1 (2)	0 (0)	ns	0 (0)	0 (0)	ns	1 (4)	0 (0)	ns	0 (0)	0 (0)	ns
M1 + E1	4 (9)	5 (5)	ns	0 (0)	1 (5)	ns	3 (13)	3 (6)	ns	1 (7)	1 (4)	ns
Chronic lesions n (%)	30 (65)	35 (37)	<0.01	6 (67)	10 (50)	ns	18 (78)	21 (45)	<0.05	6 (43)	4 (15)	ns
S1	18 (39)	22 (23)	ns	4 (44)	6 (30)	ns	10 (43)	14 (30)	ns	4 (29)	2 (7)	ns
T1/T2	12 (26)	13 (14)	ns	2 (22)	4 (20)	ns	8 (35)	6 (13)	ns	2 (14)	2 (7)	ns
(S1 + T1/T2)	9 (19)	4 (4)	<0.05	1 (11)	3 (15)	ns	7 (30)	1 (2)	<0.05	1 (7)	0 (0)	ns

Group 1 – above and *Group 2* – below the cut-off age level of 13.9 years, *A1*, *B1*, and *C1* greater degree of proteinuria, *A2*, *B2*, and *C2* smaller degree of proteinuria, *GFR* glomerular filtration rate, *M1* mesangial proliferation, *E1* endocapillary hypercellularity, *S1* segmental sclerosis; *T1* tubular atrophy/interstitial fibrosis; *ns* nonsignificant

<13.9 years with non-nephrotic range proteinuria) ($p < 0.05$).

Isolated active M1 and E1 changes were observed in 18 (39 %) children in Group 1 and 47 (50 %) children in Group 2; the difference was insignificant. Crescents were significantly more common in Group 1 than Group 2 (35 % *vs.* 18 %, $p < 0.05$); most frequently of fibrocellular and fibrous type. The presence of chronic unmodifiable S1 and T1/T2 changes was significantly more frequent in in Group 1 compared with Group 2; 30 (65 %) *vs.* 35 (37 %) of patients, $p < 0.01$, respectively. The rate of these changes did not differ significantly between age-groups of patients with nephrotic range proteinuria or isolated hematuria, but they were significantly more frequent in older children with non-nephrotic range proteinuria ($p < 0.05$).

4 Discusion

The incidence of IgAN in children in Poland is 9.3 cases *per* year, i.e., about 0.155/100,000 children *per* year, which is lower compared with the Japanese data reporting 9.9/100,000 new cases *per* year (Shibano et al. 2015) and Chinese data where one center has reported 110 cases over 12 years, albeit without giving the information on the size of the pediatric population in the area (Wang et al. 2012). According to McGrogan et al. (2011), the incidence of IgAN in children usually ranges from 0.2/100,000/year to 2.8/100,000/year. The difference in disease frequency is associated with geographic differences in genetic susceptibility to IgA nephropathy (Kiryluk et al. 2012).

The disease is more common in boys than in girls, and the male to female ratio in our registry was similar to that reported by other authors. The mean age at onset in the present study was around 11 years of age, similar to that in Japan (Shibano et al. 2015), but lower than the 16 years of age reported in China (Wang et al. 2012). The most common disease manifestations included microscopic hematuria and non-nephrotic range of proteinuria, found in 52 % of patients. Yoshikava et al. (1999) have reported 62 % of children with microscopic hematuria and proteinuria and Wang et al. (2012) have reported similar clinical findings in 47–66 % of children. Gross hematuria has been observed in 29 % of patients in the present study, as compared to 26 % of Japanese patients, 54 % of Chinese patients, and up to 80 % in different cohorts from Europe and USA (Wang et al. 2012; Yoshikava et al. 2001; Lévy et al. 1985; Linné et al. 1982).

Infections, mostly involving the upper airways, preceded urinary manifestations in 54 % of patients in the present study, similarly to the observations of other authors (Wang et al. 2012). GFR reduction at baseline, which is an established poor prognostic marker, was found in 55 % of children in the present study, significantly more frequently among older children. By using the ROC curve analysis, we were able to determine the threshold age of 13.9 years associated with worse outcomes.

Kidney biopsy was performed in all children at the mean of 1.3 years after the initial disease symptoms; significantly earlier (at 0.7 years) in older children (above 13.9 years of age). For comparison, time to kidney biopsy was 7.7 months in children and 10.7 months in adults in a study by Wang et al. (2012). Of note, chronic unmodifiable changes in kidney biopsy were significantly more frequent among older children despite a shorter time from the initial symptoms to biopsy in that group.

Some authors argue that sclerotic lesions are more characteristic for children with the presence of abnormalities in urinalysis detected earlier than a year or perhaps even 3 years before kidney biopsy, which supports the implementation of a wide urine screening program in children (Shima et al. 2015). In the present study, time to biopsy in older children (Group 1) was less than one year and sclerotic and fibrotic lesions were significantly more frequent than in the younger children (Group 2), where the time to biopsy usually exceeded one year. The greater frequency of fibrocellular or fibrous crescents and other unmodifiable chronic kidney lesions may be attributable to a longer duration of

disease. We also noted chronic lesions in biopsy specimens from children with isolated microscopic hematuria with no apparent proteinuria, which clearly speaks against the suggestions of some nephrologists to perform renal biopsy when proteinuria is greater than 0.5 g/g creatinine (Hama et al. 2015).

Due to the association between IgAN and respiratory infections, Wang et al. (2012) have recommended urinary screening, particularly in children, which might be of major meaning for early discovery of IgAN. Shima et al. (2015) have confirmed that the policy of school urinary screening is a very effective measure for prompt diagnosis and subsequent treatment of IgA nephropathy in children, preventing the development of end-stage renal disease. We conclude that IgA nephropathy may often be an insidious disease in children. The employment of mass urinary screening tests, especially after respiratory infections, has an undeniable potential to detect asymptomatic chronic renal disease in children.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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