The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults

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To study the predictive value of biopsy lesions in IgA nephropathy in a range of patient ages we retrospectively analyzed the cohort that was used to derive a new classification system for IgA nephropathy. A total of 206 adults and 59 children with proteinuria over 0.5 g/24 h/ 1.73 m^2 and an eGFR of stage-3 or better were followed for a median of 69 months. At the time of biopsy, compared with adults children had a more frequent history of macroscopic hematuria, lower adjusted blood pressure, and higher eGFR but similar proteinuria. Although their outcome was similar to that of adults, children had received more immunosuppressants and achieved a lower follow-up proteinuria. Renal biopsies were scored for variables identified by an iterative process as reproducible and independent of other lesions. Compared with adults, children had significantly more mesangial and endocapillary hypercellularity, and less segmental glomerulosclerosis and tubulointerstitial damage, the four variables previously identified to predict outcome independent of clinical assessment. Despite these differences, our study found that the cross-sectional correlation between pathology and proteinuria was similar in adults and children. The predictive value of each specific lesion on the rate of decline of renal function or renal survival in IgA nephropathy was not different between children and adults.

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Primary IgA nephropathy (IgAN) is the commonest glomerular disease in children and adolescents who undergo renal biopsy because of isolated microscopic hematuria or hematuria with non-nephrotic proteinuria.[1,2] Mild cases are surely missed as screening programs do not exist, with the exception of some Asian countries, including Japan, Korea and Taiwan.[3,4] From cohorts evaluated over relatively short follow-up, prognosis of IgAN was initially considered to be benign, but long-term studies have shown renal survival rate from time of onset of 91–93% at 10 years and 80–87% at 20 years.[5,6] In Europe, the majority of IgAN patients who start renal replacement therapy do so between the ages of 25 and 55, with 22% before the age of 30 years.[7] Given a slow decline of renal function in IgAN, many of these patients must have developed the disease as children. Identifying those at risk of progression remains difficult and clinical factors that predict outcome in adults, such as reduced renal function and persistent hypertension, are less frequent in children.[1,8–10]

Reports comparing lesions in renal biopsies of children and adults with IgAN found greater mesangial hypercellularity in children and greater glomerular sclerosis, matrix expansion, crescent formation, severe interstitial, and arteriolar changes in adults.[11–15] This observation suggests different initial pathological features and/or earlier detection in children. Furthermore, whether the predictive value of biopsy lesions in IgAN applies similarly across the age spectrum using multivariate analysis, including also clinical data, has never been investigated.

To explore this, we compared the clinicopathological features in children and adults from the cohort used by an international consensus working group to derive a new classification for IgAN, the Oxford classification.[16,17] This working group of nephrologists and pathologists has proposed that four of the six lesions (mesangial and

endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis) are predictive of outcome independent of clinical assessment. We investigated whether the predictive value of biopsy lesions in IgAN applied similarly regardless of age.

RESULTS

Children and adult clinical comparisons

Clinical assessment at the time of biopsy and during follow-up was obtained retrospectively in 59 children (median age 13 years, range 4–17.9 years) and 206 adults from Europe, Asia, and the Americas. Median follow-up time was 62 months in children and 77 months in adults ($P=0.02$). Gender and ethnicity ratios were similar in children and adults. Children were more likely than adults to have a history of macroscopic hematuria, to have lower adjusted blood pressure, to receive less antihypertensive therapy, and have higher initial estimated glomerular filtration rate (eGFR) (Table 1) but had similar proteinuria at time of biopsy. The interval between known renal abnormality and the time of renal biopsy was obtained in 228 (86%) of patients. This duration was significantly longer in adults than in children (median value of 9 months compared to 2 months in children, $P=0.027$), although the percentage of patients with duration longer than two years was similar (19% of children and 25% of adults, $P=$ ns). This subset of patients had fewer endocapillary and extracapillary lesions, and lower initial proteinuria, perhaps reflecting a milder presentation warranting greater observation time.

Children received more immunosuppressants and proteinuria was lower during follow-up. Their rate of decline in renal function was not statistically different from that of the adults, but there was a non-significant trend toward lower risk of a 50% decline in renal function or renal failure (hazard ratio 0.48, 95% confidence interval 0.20–1.13, $P=0.09$).

No significant difference was found in initial and follow-up mean arterial pressure (MAP) and proteinuria between young children ($\leqslant$13.0 years of age, 29 patients) and adolescents (age 13–17.9 years, 30 patients). Young children were more likely to being treated with immunosuppressive drugs, possibly in relation to a higher prevalence of mesangial and endocapillary hypercellularity (see below). The rate of decline in renal function was not significantly different in the two groups (-3.2 ± 12.5 versus -2.2 ± 8.5 ml/min/1.73 m^2/year).

Children and adult pathological comparisons

Histology slides from each case were reviewed by four nephropathologists in median (range 3–5) and scored for six reproducible and independent lesions identified by an iterative process.[16,17] Distributions according to age groups are shown in Figure 1. Children's biopsies showed significantly more mesangial and endocapillary hypercellularity in comparison with biopsies of adults, and young children had significantly more than that in adolescents. As expected, children had less chronic tubulointerstitial and vascular damage than adults. Interestingly, for patients in the age groups $\leqslant$13.0, 13–17.9 to 18–30 years, the prevalence of segmental glomerulosclerosis increased (0, 10.14%, respectively, $P=0.005$, trend test on quartiles using Spearman correlation), while endocapillary proliferation decreased (17, 3-0%, $P<0.001$, trend test). As expected from this observational study, presence of mesangial and endocapillary hypercellularity, and presence of crescents strongly influenced the prescription of immunosuppressants (Figure 2). Ethnicity

Table 1 | Clinical findings according to age group

	Children (n=59)	Adults (n=206)	P-value
At time of biopsy			
Median age (years)	13 (4–17.9)	35 (19–73)	
Female	25%	28%	>0.1
MAP (mm Hg)[a]	84 ± 10	102 ± 17	<0.001
eGFR (ml/min/1.73 m^2)[b]	120 ± 43	73 ± 27	<0.001
Proteinuria (g/day)[c]	2 (0.5–7.8)	1.7 (0.5–18.5)	>0.1
% Nephrotic	27%	30%	>0.1
Previous macroscopic hematuria	60%	28%	<0.001
Follow-up			
Duration of follow-up (months)	62 (20–268)	77 (12–231)	0.02
MAP (mm Hg)[a]	86 ± 8	97 ± 10	<0.001
Proteinuria (g/day)[c]	0.9 (0.1–7.0)	1.2 (0.2–9.3)	0.006
Treated with RAS blockade (ACEi, ARB)	56%	80%	<0.001
Any immunosuppression	48%	24%	0.001
Prednisone	48%	24%	0.001
Other	17%	7%	0.02
Fish oil	25%	14%	0.03
Rate of decline in renal function (ml/min/1.73 m^2/year)	−2.7 ± 11	−3.7 ± 7.6	>0.1

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; RAS, renin–angiotensin system.
[a]MAP was adjusted for gender and age for pediatric patients.
[b]eGFR was estimated using the four-variable MDRD formula for adults and the Schwartz formula for children.
[c]Proteinuria was expressed in g/24 h/1.73 m^2 in subjects aged less than 18 years and in g/day in adults (see Materials and Methods).

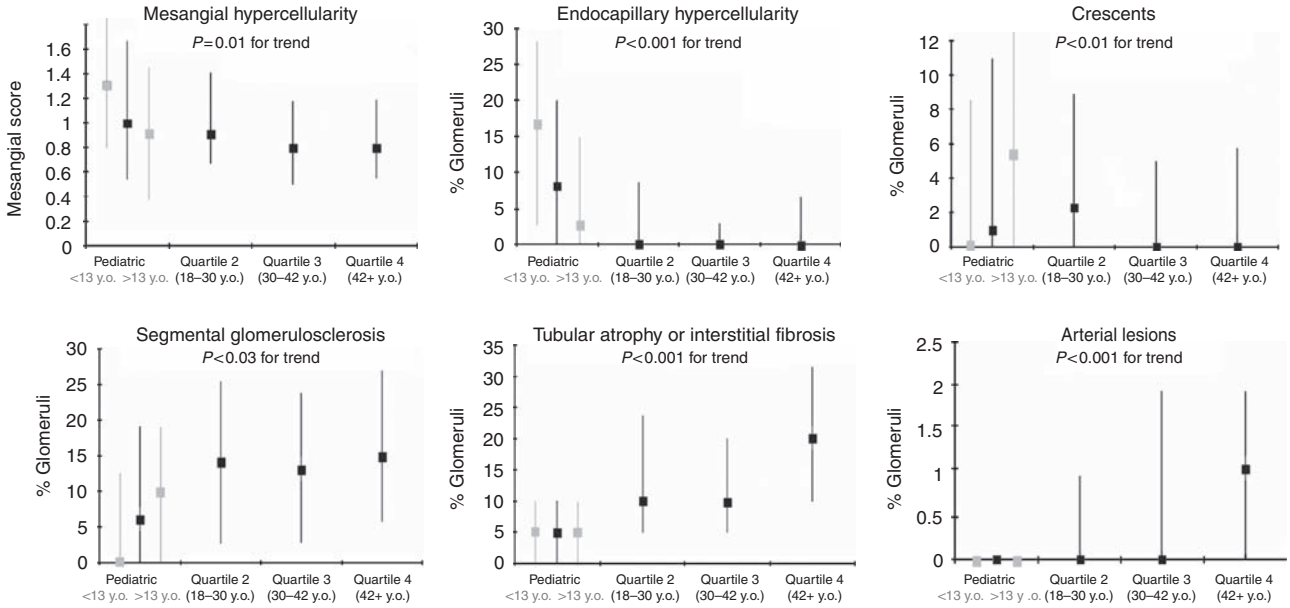

Figure 1 | Histological findings according to different age groups. Children represented 22% of the population and were considered as the first quartile for age; adult patients were divided in three groups (quartiles 2, 3, and 4). Trend test was performed on quartiles using Spearman correlation. Differences between children ⩽13.0 and adolescents are also shown and discussed in the text.

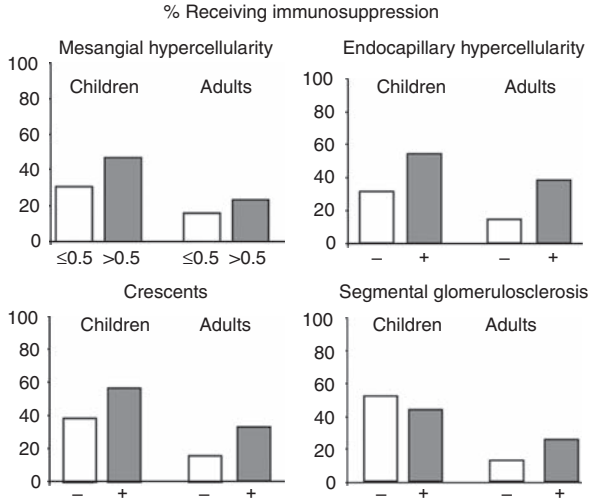

Figure 2 | Immunosuppressive treatment during follow-up.

had no significant effect on the pathological findings (Table 1). Geographical differences between children are shown in Table 2.

Clinicopathological correlations at the time of biopsy

Presence or absence of the six pre-specified lesions was not significantly associated with eGFR and MAP in children at the time of biopsy except for crescents: children with crescents had a significantly lower eGFR compared with those without ($P=0.03$). There were too few children with arterial and tubulointerstitial lesions to draw conclusions on their effect on clinical presentation (data not shown). The influence of hypercellularity (mesangial, endocapillary, and extracapillary) and segmental glomerulosclerosis lesions on the level of proteinuria was similar in adults and children (Figure 3, interaction terms with age $P>0.05$ for each lesion versus proteinuria).

A history of macroscopic hematuria was much more frequent in children than in adults (60 versus 28%, $P<0.001$). In comparison with adults, children with a history of macroscopic hematuria had more frequent (albeit not significant) endocapillary and extracapillary proliferation and fewer chronic lesions ($P<0.002$, for tubular atrophy/interstitial fibrosis). History of macroscopic hematuria did not predict rate of decline in renal function in either children or adults when analyzed separately.

Applicability of the classification in children and adults

Previous study of the whole cohort[16,17] identified four pathological variables, mesangial hypercellularity score (M0/1), segmental glomerulosclerosis (S0/1), endocapillary hypercellularity (E0/1), and tubular atrophy/interstitial fibrosis (T0/1/2), that retained predictive value in terms of renal outcome independently of clinical assessment at onset and follow-up (eGFR, MAP, and proteinuria). We performed analyses while adding an interaction term with age to verify whether the relationship between each lesion of interest and outcome was modified by age. All interaction terms were non-significant ($P>0.1$), indicating that the predictive value of pathology on the rate of decline in renal function and survival from a combined event was not modified by the age of the patient at biopsy.

Hence, children had significantly less segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and vascular lesions, and significantly more endocapillary lesions than

Table 2 | Geographical origins and clinicopathological presentation of 59 children with IgAN

	Asia	Europe (EU)	Americas (Am)	*P*-value
Number of patients	14	21	24	
Ethnicity	All Asian	All Cauc	20 Cauc, 1 AA, 3 others	
Histological findings[a]				
Mesangial hypercellularity (score)	0.9 (0.3–1.5)	0.8 (0.1–2.6)	1.4 (0.4–2.5)	0.009 Am > Asia and EU
Endocapillary hypercellularity (%)	5 (0–61)	7 (0–78)	16 (0–59)	> 0.1
Extracapillary hypercellularity (%)	1 (0–34)	5 (0–55)	3 (0–30)	> 0.1
Segmental glomerulosclerosis (%)	2.5 (0–24)	0 (0–25)	10.5 (0–50)	0.06
At time of biopsy				
Gender M/F	6/8	18/3	20/4	0.008 EU ≠ Am and Asia
Median age (years)	14 (7–17.9)	13 (4–17.9)	13 (7–17.9)	> 0.1
GFR initial (ml/min/1.73 m^2)	146 ± 51	102 ± 30	120 ± 37	0.01 Asia > EU
MAP initial (mm Hg)	77 ± 10	88 ± 10	85 ± 8	0.02 Asia < EU and Am
Proteinuria initial (g/day/1.73 m^2)	2.1 (0.5–6.2)	1.5 (0.6–5.1)	2.5 (1.1–7.8)	> 0.1

Abbreviations: GFR, glomerular filtration rate; IgAN, IgA nephropathy; MAP, mean arterial pressure.
[a]Tubular atrophy/interstitial fibrosis and arterial lesions are not reported, because they were rare in children.
Cauc, Caucasian; AA, African American; others, other ethnicities.

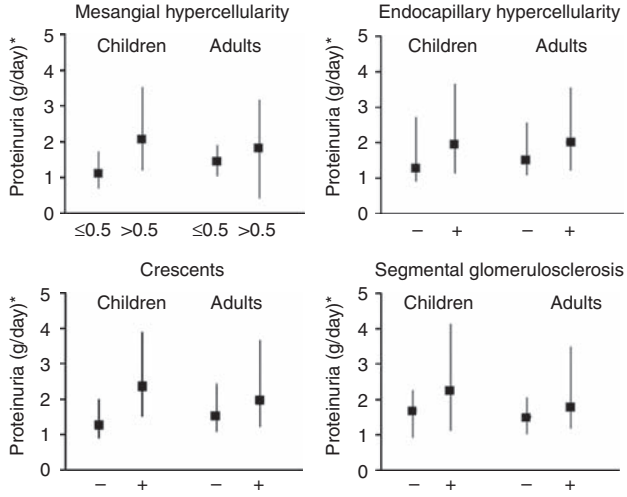

Figure 3 | Correlation between proteinuria and histological findings. *Proteinuria was expressed in g/24 h/1.73 m^2 for subjects aged less than 18 years and in g/day in adults (see Materials and Methods).

adults. These differences in the prevalence of lesions contributed to a distinctly different prognosis between children and adults. However, the predictive value of each pathological variable on outcome was similar regardless of age (Table 3). For instance, in children and adults, those whose renal biopsies had minimal mesangial changes (M0), mesangial hypercellularity (M1), and no endocapillary proliferation (E0) showed different slopes of eGFR according to the presence or absence of segmental glomerulosclerosis (S1) (Table 3), showing that the classification is valid in both age groups.

DISCUSSION

The proposed Oxford clinicopathological classification provides a new predictive tool on the basis of the lesions detected at renal biopsy in patients with IgAN. While the traditional approach to a classification was to list a series of relevant lesions and group them according to expert opinions, the proposed classification was determined using a methodology that sequentially assessed reproducibility, colinearity, optimal categorization, and independence from clinical assessment.[16,17]

To assess the validity of the new Oxford classification of IgAN in children, we took advantage of the wide age spectrum of patients from the original cohort, all provided with a renal biopsy suitable for reviewing and a complete data set expanded over a long follow-up. This careful data collection procedure was lacking in previous cohorts and limited the clinical evaluation;[15] we paid particular attention to homogenizing units of measurement to allow comparison of data in children and in adults, looking for the predictive value of histological lesions in renal outcome.

As expected, children presented with a higher eGFR and more frequent history of macroscopic hematuria. Given our entry criteria, children and adults had similar baseline levels of proteinuria. The rate of decline in renal function was also similar in the two age groups, although the frequency of progression to the end point of decline in renal function or renal failure tended to be higher in adults. This finding suggests a common natural history for children and adults with IgAN, with a similar rate of progression. Adults detected later in the clinical course than children would likely reach the final end point more rapidly, having a lower initial eGFR at the time of renal biopsy. However, important divergences between children and adults must be emphasized.

First, differences in histological features should not be disregarded and remarkable changes in lesion prevalence were observed with increasing age despite similar initial proteinuria. Highest mesangial and endocapillary hypercellularity were found in younger children and progressively decreased in adult age. Crescents were also more frequent at younger age. In contrast, glomerular sclerosis, tubular/interstitial fibrosis, and arteriosclerotic lesions were more prevalent in older subjects. These features depict a disease with greater active lesions in children, at least at similar levels

Table 3 | Applicability of the Oxford classification to children and adults

	Children (n=59)			Adults (n=206)		
	No. of patients	Slope (ml/min/1.73 m^2/year)	s.d.	No. of patients	Slope (ml/min/1.73 m^2/year)	s.d.
M0, S0, E0	3	1.5	4.1	10	0.5	2.0
M0, S1, E0	4	−3.4	5.3	18	−1.1	1.8
M1, S0, E0	4	−2.0	5.7	27	−2.3	4.2
M1, S1, E0	10	−5.7	10.1	78	−4.5	7.3
M0/1, S0, E1	16	1.4	13.5	5	0.4	3.9
M0/1, S1, E1	22	−5.0	10.0	68	−4.9	10.0

M0=Mesangial hypercellularity score $\leqslant$0.5.
M1=Mesangial hypercellularity score $>$0.5.
S0=Segmental glomerulosclerosis: Absent.
S1=Segmental glomerulosclerosis: Present.
E0=Endocapillary hypercellularity: Absent.
E1=Endocapillary hypercellularity: Present.

of initial proteinuria. Whether this can be generalized to all IgAN patients is unknown as adult and pediatric participating centers may have different referral biases and did not report the proportion of subjects screened that fulfilled the entry criteria.

Second, younger patients received considerably more immunosuppressive drugs during follow-up. This could explain the lower follow-up proteinuria in children and may influence the outcome. Given this, the rate of renal function decline in children can be difficult to compare with that in adults. It is possible, had no therapy been given, that children would have experienced a significantly faster rate of decline in renal function. In contrast, a recent report considering only patients with IgAN and proliferative changes, showed better renal survival in children or adolescents as compared with that in adults.[15] Although of clinical importance, we remain very cautious in our interpretation of the risk of progression in children.

The main thrust of this study was not to compare children with adults with regards to outcome but to verify whether the information at renal biopsy had a similar meaning in both age groups. At the time of biopsy, cross-sectional correlations between pathological findings and proteinuria were similar in both age groups supporting the applicability of this classification. Furthermore, during follow-up, the rate of decline in renal function was similar in the two age groups even when a combination of scores for different lesions was considered. The multivariate analysis showed that the predictive value of the four renal features (mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis) was independent not only from clinical data at renal biopsy but even from data during follow-up. Notably, the value of the four variables identified in the Oxford Consensus Classification for prediction of final outcome was not influenced by the age of the patients at renal biopsy using interaction studies, supporting its applicability irrespective of age.

There are several limitations to this study. It is retrospective in nature and has a selection bias due to enrolment of patients with potentially progressive renal course but excluding rapidly progressive cases. The number of children is limited; hence the subgroup analysis comparing children with adults may be underpowered. However, it is noteworthy that the rates of renal function decline in Table 3 estimated using combinations of pathological findings are very similar to adults. Sub-analysis of race and ethnicity is also underpowered. However, the findings from our unique cohort with its age spectrum, analyzed by a multivariate analysis approach with carefully checked clinical data not only at renal biopsy but also during follow-up, support the value of the conclusions derived. Validation studies are being undertaken in North America, Europe, and Asia. A single clinicopathological classification for all subjects with IgAN, independent of age, will facilitate the design of clinical trials and the generalization of their results.

MATERIALS AND METHODS

Pathology definitions

Six pathological variables were selected on the basis of reproducibility among pathologists, least susceptibility to sampling error, and ease of scoring in routine practice while avoiding strong colinearity.[16] The selected variables included in the analysis were mesangial hypercellularity, segmental glomerulosclerosis or adhesion, endocapillary hypercellularity, cellular or fibrocellular crescents, tubular atrophy/interstitial fibrosis, and arterial intimal thickening. Continuous variables were also studied as categorical to facilitate the classification. Receiver operating characteristics curves were plotted for each variable to determine the optimal cut-offs predicting a worse outcome (the most clinically relevant outcome was the rate of decline in renal function, dichotomized to perform this analysis). The cut-off for mesangial hypercellularity score was 0.5 (equivalent to 50% of glomeruli showing mild mesangial hypercellularity); segmental glomerulosclerosis, endocapillary hypercellularity, and extracapillary proliferation were best categorized as present or absent; tubular atrophy/interstitial fibrosis and arterial lesions were categorized as absent/mild (0–25%), moderate (26–50%), or severe ($>$50%). Therefore, it was concluded that these features should be summarized and scored as follows:

Mesangial score $\leqslant$0.5 (M0) or above (M1)
Endocapillary hypercellularity absent (E0) or present (E1)

Segmental glomerulosclerosis absent (S0) or present (S1)
Tubular atrophy/interstitial fibrosis ⩽25% (T0), 26–50% (T1), or >50% (T2)

Selection of patients

Patients with biopsy-proven IgAN (defined by standard criteria, including predominant, or codominant mesangial deposition of IgA) were included regardless of treatment given. Cases with advanced renal insufficiency (initial eGFR < 30 ml/min per 1.73 m^2) were excluded as well as those with <12 months of follow-up to minimize error in the estimation of the rate of renal function decline over a short period of time, recognizing this was likely to exclude the most acute and rapidly progressive cases. We also excluded subjects with proteinuria <0.5 g/24 h per 1.73 m^2, who are known to be at low risk of progression, as well as secondary causes of mesangial IgA deposits such as Henoch–Schönlein purpura and patients with diabetes mellitus.

Clinical data set

Gender, ethnicity, and age at the time of biopsy were noted. Children were defined as subjects aged <18 years at biopsy. For some analyses children ⩽13.0 years at biopsy and adolescents were considered separately.

Clinical parameters collected within 3 months of the date of biopsy and during follow-up included systolic and diastolic blood pressure, weight, height, serum creatinine, and 24-h urine protein or urine protein-to-creatinine ratio (UP/UCr). Children had a median number of 8 blood pressure, 7 serum creatinine, and 8 proteinuria measurements per subject and adults had 7, 6, and 7 measurements, respectively.

To provide consistency between measurements in adults and children, and as patients progressed from pediatric age to adulthood, proteinuria was expressed in g/24 h per 1.73 m^2 in subjects aged less than 18 years. When 24-h urine protein was not available, UP/UCr (mg/mg) was considered as an estimate of 24-h protein excretion adjusted for body surface area. UP/UCr was used almost exclusively in children, representing 42% of all proteinuria measurements in that group. Proteinuria was considered in the nephrotic range when was >3 g/24 h per 1.73 m^2 or when UP/UCr > 3.

Blood pressure was adjusted for gender and age in children. For each child the standard deviation score for MAP was calculated for each measurement using gender-specific constants interpolated for the child's age;[18] MAP was then recalculated from the standard deviation score using the appropriate constants for an adult subject.

eGFR was estimated for children using the four-variable MDRD formula in adults and the Schwartz formula.[19,20] To avoid sudden artificial changes in eGFR and to simplify the estimation of the rate of renal function decline (see below), we did not switch from the Schwartz to the MDRD equation for an individual or change the Schwartz constant from 0.55 to 0.70 for adolescent boys (29 patients); in 6 adolescent boys aged 17 years at the time of biopsy, only the MDRD equation was used.

Treatment modalities reported were immunosuppressive agents, fish oil, and several antihypertensive medications, including renin–angiotensin blockade using an angiotensin-converting enzyme inhibitor or using angiotensin-receptor blockers. These were reported as intent to treat regardless of the type or duration of therapy. Data were verified by communication between two of the lead authors (S Troyanov and R Coppo) and contributing centers.

Definitions

End-stage renal disease was defined as eGFR < 15 ml/min per 1.73 m^2. MAP was defined as diastolic pressure plus a third of the pulse pressure. For each patient, average MAP and proteinuria were determined for each year of observation. Follow-up MAP and proteinuria represent the average of these respective values.

Statistical methods

Normally distributed variables were expressed as mean ± standard deviation and compared using Student's *t*-test, one-way analysis of variance, or Pearson test. Non-parametric variables were expressed as median and range, and compared using Mann–Whitney, Kruskal–Wallis, or Spearman test. Categorical variables were expressed in percentages and compared using Pearson χ^2-test.

Different clinical outcomes were studied to address the predictive value of the pathological variables. The rate of decline in renal function for each patient was determined by fitting a straight line through available data for eGFR using the principle of least squares. One outlier was censored by visual inspection of line fits in six subjects. We also studied survival from a combined event (50% reduction in renal function or end-stage renal disease) using univariate Cox regression.

The influence of age or ethnicity on the relation between pathology and the rate of renal function decline was studied using general linear and survival models with interactions terms. All *P*-values were two-tailed and values less than 0.05 were considered statistically significant. Confidence intervals included 95% of predicted values. Analyses were peformed using SPSS software (version 11; SPSS, Chicago, IL, USA).

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Coppo R. Pediatric IgA nephropathy: clinical and therapeutic perspectives. *Semin Nephrol* 2008; **28**: 18–26.
2. Coppo R, Gianoglio B, Porcellini MG *et al.* Frequency of renal diseases and clinical indications for renal biopsy in children. *Nephrol Dial Transplant* 1998; **13**: 293–297.
3. Yamagata K, Takahashi H, Tomida C *et al.* Prognosis of asymptomatic hematuria and/or proteinuria in men. High prevalence of IgA nephropathy among proteinuric patients found in mass screening. *Nephron* 2002; **91**: 34–42.
4. Lee YM, Baek SY, Kim DS *et al.* Analysis of renal biopsies performed in children with abnormal findings in urine mass screening. *Acta Paediatr* 2006; **95**: 849–853.
5. Hastings MC, Delos Santos NM, Wyatt RJ. Renal survival in pediatric patients with IgA nephropathy. *Pediatr Nephrol* 2007; **22**: 317–318.
6. Ronkainen J, Ala-Houhala M, Autio-Harainen H *et al.* Long-term outcome 19 years after childhood IgA nephritis: a retrospective cohort study. *Pediatr Nephrol* 2006; **21**: 1266–1273.
7. Fassbinder W, Brunner FP, Brynger H *et al.* Combined report on regular dialysis and transplantation in Europe, XX, 1989. *Nephrol Dial Transplant* 1991; **6**: 5–35.
8. Coppo R, D'Amico G. Factors predicting progression of IgA nephropathies. *J Nephrol* 2005; **18**: 503–512.
9. Yoshikawa N, Ito H, Nakamura H. Prognostic indicators in childhood IgA nephropathy. *Nephron* 1994; **60**: 60–67.
10. Hogg RJ, Silva FG, Wyatt RJ *et al.* Prognostic indicators in children with IgA nephropathy. Report of the Southwest Pediatric Nephrology Study Group. *Pediatr Nephrol* 1994; **8**: 15–20.
11. Ikezumi Y, Suzuki T, Imai N *et al.* Histological differences in new-onset IgA nephropathy between children and adults. *Nephrol Dial Transplant* 2006; **21**: 3466–3474.
12. Kusumoto Y, Takebayashi S, Taguchi T *et al.* Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and in adult Japanese. *Clin Nephrol* 1987; **28**: 118–124.
13. Okada K, Funai M, Kawakami K *et al.* IgA nephropathy in Japanese children and adults: a comparative study of clinicopathologic features. *Am J Nephrol* 1990; **10**: 191–197.
14. Mina SN, Murphy WM. IgA nephropathy. A comparative study of the clinicopathologic features in children and adults. *Am J Clin Pathol* 1985; **83**: 669–675.
15. Haas M, Rahman MH, Cohn RA. IgA nephropathy in children and adults: comparison of histologic features and clinical outcomes. *Nephrol Dial Transplant* 2008; **23**: 2537–2545.
16. Roberts IS, Cook HT, Troyanov S *et al.* The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int* 2009; **76**: 546–556.
17. Cattran DC, Coppo R, Cook HT *et al.* The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009; **76**: 534–545.
18. Wühl E, Witte K, Soergel M *et al.* Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. *J Hypertens* 2002; **20**: 1995–2007.
19. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–470.
20. Work DF, Schwartz GJ. Estimating and measuring glomerular filtration rate in children. *Curr Opin Nephrol Hypertens* 2008; **17**: 320–325.