



Clinical and histological differences between adults and children in new onset IgA nephropathy

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Received: 2 October 2019 / Revised: 5 May 2020 / Accepted: 12 May 2020 / Published online: 22 May 2020
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Abstract

Background Previous reports suggest initial presentation of IgA nephropathy (IgAN) in children is different from adults. No systematic comparison of clinical, biological, and histological childhood- and adult-onset IgAN is currently available.

Methods We compared pediatric and adult clinical and histological characteristics at IgAN diagnosis. Data on 211 consecutive patients from two different centers in Paris (82 children, 129 adults) were reviewed. Kidney biopsies were scored for Oxford classification and podocytopathic (P1) features.

Results We report higher eGFR at diagnosis in children compared to adults (89.5 vs. 64 ml/min/1.73 m²; $p = 0.0001$) but no difference in proteinuria. Histological analysis of kidney biopsy found higher proportions of mesangial (M1) and endocapillary (E1) hypercellularity in children compared with adults (M1 [80.7% vs. 27.9%, $p = 0.0001$]; E1 [71.3% vs. 30%, $p = 0.0001$]). Focal glomerulosclerosis (S1), tubular atrophy/interstitial fibrosis $\geq 25\%$ (T1), and P1 were more frequent in adults (S1 [81.5% vs. 61.3%, $p = 0.0012$], T1 [49.5% vs. 1.35%, $p = 0.0001$], P1 [33.8% vs. 16.4%, $p = 0.008$]). Proteinuria associated with M1, E1, and C1 in children (M1, $p = 0.0001$; E1, $p = 0.0005$; C1, $p = 0.0014$) but S1, P1, and T1 in adults (S1, $p = 0.0001$; P1, $p = 0.0001$; T1, $p = 0.001$). After steroid treatment (41 children and 28 adults), proteinuria decreased in children ($p < 0.001$, follow-up 38 months) and adults ($p < 0.001$, follow-up 76.9 months), whereas eGFR remained stable in adults but increased significantly in children (90.6 to 110 ml/min/1.73m²).

Conclusion Proteinuria in children with IgAN is a marker of glomerular proliferative lesions whereas its presence in adults often reflects the presence of chronic lesions. This suggests the need for histological assessment.

Keywords IgA nephropathy · Primary glomerulonephritis · Kidney biopsy · Presentation · Children · Adults · Oxford classification

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Introduction

Pediatric IgA nephropathy (IgAN) can be considered one of the most common types of primary glomerulonephritis in children worldwide [1, 2]. Although IgAN is characterized morphologically by glomerular deposits of IgA, there are different manifestations of the disease with a huge spectrum of clinical presentations, ranging from isolated hematuria to acute nephritis, with rapid deterioration of kidney function leading to kidney failure. Histologically, renal lesions are the most common presentation and consist of focal or diffuse mesangial proliferative glomerulonephritis with a different histologic variability, from minimum histologic lesions by light microscopy to proliferative glomerulonephritis. IgAN may be paucisymptomatic, and diagnosis may only be made after the detection of a small deterioration in glomerular filtration rate (GFR) or the diagnosis of hypertension, which are markers of an unfavorable prognosis in children and adults [3–7]. IgAN is particularly more frequent in young adults, but the median age of patients reaching dialysis is about 50 years, suggesting a silent disease progression for many years and a potential origin in childhood. Pediatric IgAN has long been considered a benign disease [8, 9] with frequent remissions in childhood and sometimes late relapses in adulthood [10]. Nevertheless, a pediatric cohort has shown that 10–13% of children would reach stage 5 chronic kidney disease (CKD) within 10 years and within 20 years 20–30% would reach stage 5 CKD, close to that observed in adult patients [10–12]. Adult IgAN is considered a serious disease with 15–40% of patients progressing to stage 5 CKD after 20 years' follow-up [13, 14]. It is relevant to determine if there are clinical and histological differences at onset presentation in the course of adult versus pediatric IgAN. A younger age has been reported as an independent predictor of poor outcome and deterioration of renal function [14]. It is noteworthy that previous publications have reported that histological features at onset of IgAN are different in children and adults [15, 16]. Pediatric patients would more likely have proliferative lesions and less advanced chronic lesions (glomerulosclerosis and/or interstitial fibrosis/tubular atrophy) [15, 17, 18]. However, the differences or similarities between pediatric and adult IgAN remain unclear [19]. The primary objective of this study was to compare clinical, biological, and histological characteristics at time of IgAN diagnosis between children and adults in this French cohort. A secondary objective was to compare steroid-sensitivity between children and adults in the groups investigated.

Patients and methods

Patients

A total of 211 patients, with 82 children (defined as ≤ 18 years old) and 129 adults (> 18 years old), with biopsy-proven IgAN from Necker Hospital (adult and pediatric Nephrology Departments) and Robert Debré Hospital between 1990 and 2015 were retrospectively analyzed. The ethics committee of St Antoine Hospital in Paris, France, approved the study for pediatric and adult centers. This pediatric cohort was previously described [20]. The diagnosis of IgAN was established by detection of mesangial deposition of polyclonal IgA as the predominant or co-dominant immunoglobulin by immunofluorescence microscopy. Patients with systemic diseases, such as systemic lupus erythematosus, IgA vasculitis, chronic liver diseases, and minimal change disease associated with IgA nephropathy were excluded.

Clinical data set

Children were aged < 18 years at biopsy. Relevant clinical and biological parameters were retrospectively collected at the time of biopsy (within 3 months of the date of biopsy) and during follow-up (including age, sex, weight, height, clinical presentation at disease onset, systolic and diastolic blood pressure, serum albumin, serum IgA levels, serum creatinine [SCr, expressed in $\mu\text{mol/L}$], estimated GFR (eGFR), urine protein-to-creatinine ratio [g/g], used as an estimation of 24-h protein excretion adjusted for body surface area). For children, eGFR was estimated using the Schwartz equation: $\text{creatinine clearance (ml/min/1.73 m}^2) = K \times L/\text{SCr}$ where L is body length (cm), and $K = 41.3$ [21, 22]. A maximum eGFR set at 120 ml/min/1.73 m^2 was selected as the accuracy of eGFR for higher values and to avoid the disproportionate impact of small variations in creatinine on the rate of kidney function variation [22]. For adults, eGFR was calculated using the modification of diet in renal disease (MDRD) equation. Nephrotic syndrome was diagnosed with a serum albumin < 3 g/dL and protein excretion ≥ 3 g/g creatinine. Definition of acute kidney injury was an eGFR below 70 ml/min/1.73 m^2 with proteinuria and/or hematuria. Definition of stage 5 CKD was an eGFR < 15 ml/min/1.73 m^2 or the need for kidney transplantation. Microscopic hematuria was defined by the presence of more than five erythrocytes per field of view, and macroscopic hematuria was established by the presence of gross hematuria. Complete clinical remission was defined by proteinuria at the last follow-up < 0.3 g/g creatinine with eGFR > 90 ml/min/1.73 m^2 .

Histopathology

In the present analysis, all pediatric and adult IgAN kidney biopsies were re-analyzed for this study by two renal pathologists (MR and MP) and scored for every feature according to the full Oxford score. Some biopsies were not analyzable for all histological variables. Variables of the Oxford classification [23, 24] have been analyzed, and six were used: mesangial hypercellularity (M), scored as absent (M0) or (M1) if $\geq 50\%$ of glomeruli had more than three cells per mesangial area; segmental glomerulosclerosis or adhesion (S), scored (S0) if absent or (S1) if present; podocyte hypertrophy or sclerosis at the tubular pole (tip lesion) was referred to as podocytopathies (P), scored as absent (P0) or present (P1) using the Columbia Working Group definition [25]; endocapillary hypercellularity (E), scored as E0 if absent or E1 if present; extracapillary hypercellularity (C) including cellular, fibrocellular, or fibrous crescent scored as C0 (no crescents), C1 (crescents in at least one but $< 25\%$ of glomeruli), or C2 (crescents in more than 25% of glomeruli); tubular atrophy/interstitial fibrosis (T), T0/T1/T2 as the degree of tubular atrophy or interstitial fibrosis ($< 25\%$, $25\text{--}50\%$, $> 50\%$, respectively) [16].

Steroids in pediatric and adult IgAN

Drug exposure was recorded, including immunosuppressive agents such as steroids, fish oil, and the administration of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

In pediatric IgAN, steroids were used as previously described [20]. In the adult cohort, steroids were used in patients with persistent proteinuria defined as urinary protein excretion of at least 0.5 g per day with renin-angiotensin system blockade (RASB) therapy for at least 6 months. Patients received either pulse steroid therapy then oral therapy with reduction over 6 months or oral steroid alone.

Statistical analysis

Normally distributed variables were written as mean \pm standard deviation (SD) and compared with one-way analysis of variance (ANOVA) or Student's *t* test. Non-parametric variables were written as median with interquartile range and compared using either the Kruskal–Wallis or the Mann–Whitney test. Categorical variables were compared and written as percentages using the Pearson χ^2 test.

Results

Comparison of clinical, biological, and pathological characteristics at diagnosis

Males represented 65.8% and 73.8% of children and adults, respectively. Age at diagnosis was 10.6 (± 0.4) years in children and 39.1 (± 1.1) years in adults. Fifteen children (18.2%) and 12 adults (9.6%) had a suspected or proven family history of IgAN. The mean systolic and diastolic blood pressure in children and adults, respectively, was 115.55 (± 15.5)/67.6 (± 11.6) mmHg and 136.5 (± 19.7)/80.6 (± 13.2) mmHg. Diagnostic mean eGFR was higher in children compared with adults, respectively (89.5 vs. 64 ml/min/1.73 m²; $p = 0.0001$), and serum albumin level was lower in children compared with adults (3.4 vs. 3.8 g/dl, $p = 0.0001$). Proteinuria was not different between children and adults, respectively (2.1 vs. 1.8 g/g of creatinuria, $p = 0.25$) (Table 1). Frequency of hematuria was significantly higher in children compared to adults (100% vs. 36%, $p = 0.0001$).

Analysis of kidney biopsy findings reveals a higher proportion of M1 and E1 lesions in children compared with adults, respectively (M1 [80.7% vs. 27.9%, $p = 0.0001$]; E1 [71.3% vs. 30%, $p = 0.0001$]). Extracapillary hypercellularity was different between children and adults (C0 53.4% vs. 64.4%; C1 35.6% vs. 33.3%; C2 11% vs. 2.3%, $p = 0.11$). Focal glomerulosclerosis/adhesion (S1), tubular atrophy/interstitial fibrosis $\geq 25\%$, and podocytopathic features (P1) were lower in children compared with adults, respectively (S1 [61.3% vs. 81.5%, $p = 0.0012$], T1 [1.35 vs. 49.5%, $p = 0.0001$], P1 [16.4% vs. 33.8%, $p = 0.008$] (Table 1).

Associations between histological findings and clinico-biological features at time of kidney biopsy

Proteinuria was associated with M1, E1, and C1 in children (M1, $p = 0.0001$; E1, $p = 0.0005$; C1, $p = 0.0014$) whereas proteinuria was associated with S1, P1, and T1 in adults (S1, $p = 0.0001$; P1, $p = 0.0001$; T1, $p = 0.001$) (Table 2, Fig. 1). Proteinuria increased significantly with the association of full proliferation lesions (M1; E1; C1) to reach nephrotic range only in children ($p < 0.0001$). In adults, proteinuria increased to more than 2 g/g when 2 proliferative lesions were present but did not reach nephrotic range proteinuria (Fig. 1). Linear regression revealed a significant association between proteinuria and number of proliferative lesions only in children. The regression coefficient of 1.148 reflects the fact that each

Table 1 Comparison of clinical and biological characteristics between children and adults at time of biopsy

Variable ^a	Adult (n = 129)	Children (n = 82)	P value
Age at diagnosis (years)	39.1 ± 1.1	10.6 ± 0.4	0.0001
Familial IgAN history	11 (9.6)	15 (18.3)	0.07
Male	99 (73.8)	54 (65.8)	0.2
Systolic BP (mmHg)	136.46 ± 19.7	115.55 ± 15.5	
Diastolic BP (mmHg)	80.6 ± 13.2	67.6 ± 11.6	
eGFR (ml/min/1.73m ²)	64 ± 29.1	89.5 ± 31.8	0.0001
Serum albumin (g/dl)	3.8 ± 0.6	3.4 ± 0.7	0.0001
Proteinuria (g/g of creatinuria)	1.8 ± 1.6	2.1 ± 2.7	0.25
Pathological findings			
Glomerulus count	15.1 ± 7.9	15.9 ± 8.2	0.5
• M1	36 (27.9)	63 (80.7) (n = 78)	0.0001
• E1	39 (30)	57 (71.3) (n = 80)	0.0001
• C1/C2	43 (33.3)/3 (2.3)	26 (33.7)/8 (10.3) (n = 77)	0.11
• S1	106 (81.5)	49 (61.3) (n = 80)	0.0012
• P 1	44 (33.8)	12 (16.4) (n = 73)	0.0077
• T1	63 (49.5)	1 (1.35) (n = 74)	0.0001

^a For quantitative variables, values are expressed as mean ± SD [standard deviation]. For qualitative variables, values are expressed as n (%)

C1, crescents in at least one but < 25% of glomeruli; *C2*, crescents in more than 25% of glomeruli; *eGFR*, estimated glomerular filtration rate; *E1*, presence of endocapillary hypercellularity; *IgAN*, IgA nephropathy; *M1*, presence of mesangial hypercellularity; *P1*, presence of podocytopathy; *S1*, presence of segmental glomerulosclerosis or adhesion; *systolic BP and diastolic BP*, systolic and diastolic blood pressure; *T1*, presence of tubular atrophy/interstitial fibrosis > 25%

proliferative lesion significantly increases proteinuria by an average of 1.148 g/g ($p < 0.0001$). In adults, only non-proliferative lesions were associated with proteinuria. The regression coefficient of 0.8806 reflects an average increase of proteinuria by 0.8806 g/g for each non-proliferative lesion ($p < 0.0001$) (Fig. 1 and 2). Podocytopathic features were associated with age at diagnosis for children and were significantly more prevalent in older children ($p = 0.001$), while tubular atrophy/interstitial fibrosis was associated with age at diagnosis for adults ($p = 0.012$).

Comparison of steroid response in adults and children

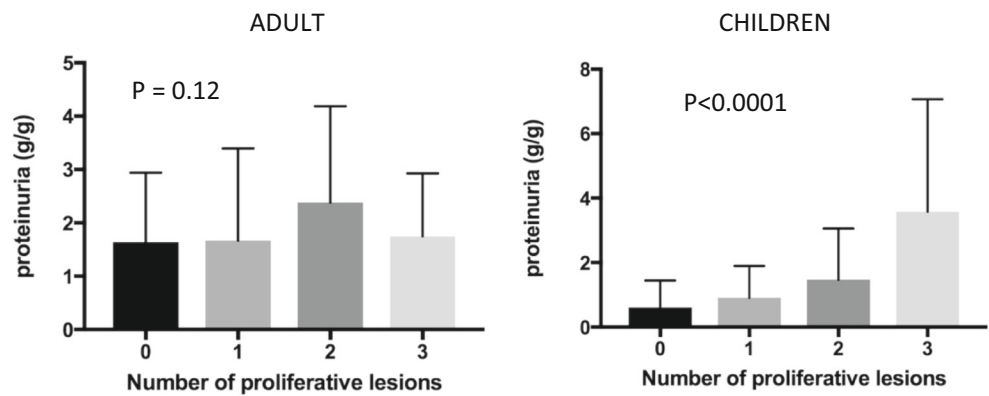
We analyzed 41 children and 28 adults treated with steroids and excluded those treated with other immunosuppressive agents. RASB treatment was introduced after diagnosis for the entire adult group and for 93.3% of the pediatric cohort. Children had a higher proportion of M1 and E1 lesions, while S1 and T1/2 lesions were lower compared to the adult group, respectively (87.2% vs 39.3% ; 77.5% vs 39.3% ; 60% vs 92.9% ; 21.4/50 vs 0/0). C1/2 lesion was not different between children and adults (42.2/10.5 vs 67.9/7.1). Average duration

Table 2 Associations between pathological and clinico-biological features at time of biopsy in children and adults

	Active lesions						Chronic lesions					
	M0 vs M1		E0 vs E1		C0 vs C1		S0 vs S1		P0 vs P1		T0 vs T1 vs T2	
	P		P		P		P		P		P	
	Children	Adult	Children	Adult	Children	Adult	Children	Adult	Children	Adult	Children	Adult
eGFR (ml/min/1.73 m ²)	0.5	0.15	0.8	0.17	0.2	0.17	0.6	0.18	0.8	0.0026	NS	0.001
Proteinuria (g/g)	0.0001	0.24	0.0005	0.9	0.0014	0.13	0.6	0.0001	0.37	0.0001	NS	0.001
Age at diagnostic (years)	0.1	0.9	0.11	0.29	0.15	0.034	0.13	0.55	0.0001	0.56	NS	0.017

C1 presence or *C0* absence of extracapillary proliferation; *eGFR*, estimated glomerular filtration rate; *E1* presence or *E0* absence of endocapillary hypercellularity; *M1* presence or *M0* absence of mesangial hypercellularity; *NS*, non-statistical significance for only 1 child; *P1* presence or *P0* absence podocytopathic features; *S1* presence or *S0* absence of segmental glomerulosclerosis or adhesion; *T1*, presence of tubular atrophy/interstitial fibrosis > 25%; *T2*, presence of tubular atrophy/interstitial fibrosis > 50%

Fig. 1 Association between proliferative lesions and proteinuria at time of biopsy



of follow-up was different for both children and adults, respectively 38 [24–67] and 76.9 [45.4–105.4] months ($p = 0.008$). After steroid treatment, proteinuria at last follow-up decreased in children (1.6 [1–3.2] to 0.03 [0.01–0.1] g/g, $p < 0.001$) and in the adult group (1.65 [1–2.6] to 0.4 [0.2–0.95] g/g, $p = 0.0017$) between M0 and the last follow-up. eGFR increased significantly in children (90.6 [72.3–120] to 110 [94.6–120.9] ml/min/1.73 m²) and decreased slightly in adults (41.4 [34.6–62.8] to 36.9 [17.9–62.3] ml/min/1.73 m², $p = 0.01$) (Fig. 3).

Discussion

The present study compares clinical, biological, and histological characteristics between children and adults with biopsy-proven IgAN at diagnosis in a cohort from two important French centers. It reveals that pediatric IgAN is more likely an acute glomerulonephritis without the chronic lesions found in adults; it is reflected in higher frequencies of an acute nephritic/nephrotic syndrome and acute kidney injury at baseline clinical conditions. The clinico-pathological approach revealed an equivalent proteinuria in both groups but without the same pattern of histological lesions. Kidney biopsy was used to establish clinico-pathological correlations between pathological findings and clinico-biological manifestations. Here, we reveal that proteinuria is a hallmark of disease activity with potentially reversible injury in children; while in

adults, it is an indication of disease chronicity with irreversible scarring. The prognostic effect of the T lesion, which is the most powerful histological variable in the Oxford classification, cannot be assessed in children [23]. Steroids would appear to be more beneficial in acute glomerulonephritis with few chronic lesions.

eGFR at diagnosis was lower and serum albumin was higher in adults compared with children as was also found in the studies by Ikezumi et al. and Wang et al. [15, 17]. Mostly, studies have concluded that children with IgAN are more likely to have a benign outcome compared with adults, but in fact, this is probably due to the delayed diagnosis of adult IgAN.

Our results show that pediatric IgAN has a different histological assessment from adults, with higher histologic proliferation and glomerular inflammation, and fewer chronic lesions. Nevertheless, the origin of this proteinuria seems to be different. In the pediatric context, proteinuria is probably due to proliferation and inflammation, while in adults it is more likely linked to chronic lesions and nephrotic reduction. In our study, proteinuria was associated with M1, E1, and C1 in children but with S1, P1, and T1 in adults. Proteinuria also increases significantly with the association of proliferation lesions to reach nephrotic range only in children. Histological analysis of kidney biopsies found 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 $\geq 25\%$ and podocytopathic

Fig. 2 Association between non proliferative lesions and proteinuria at time of biopsy

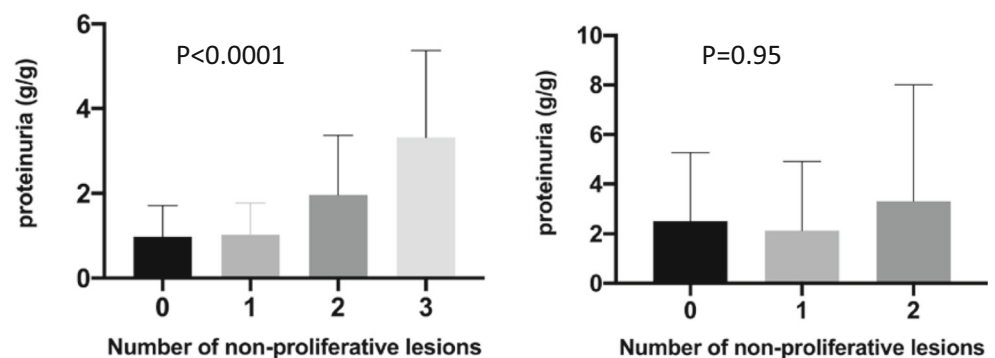
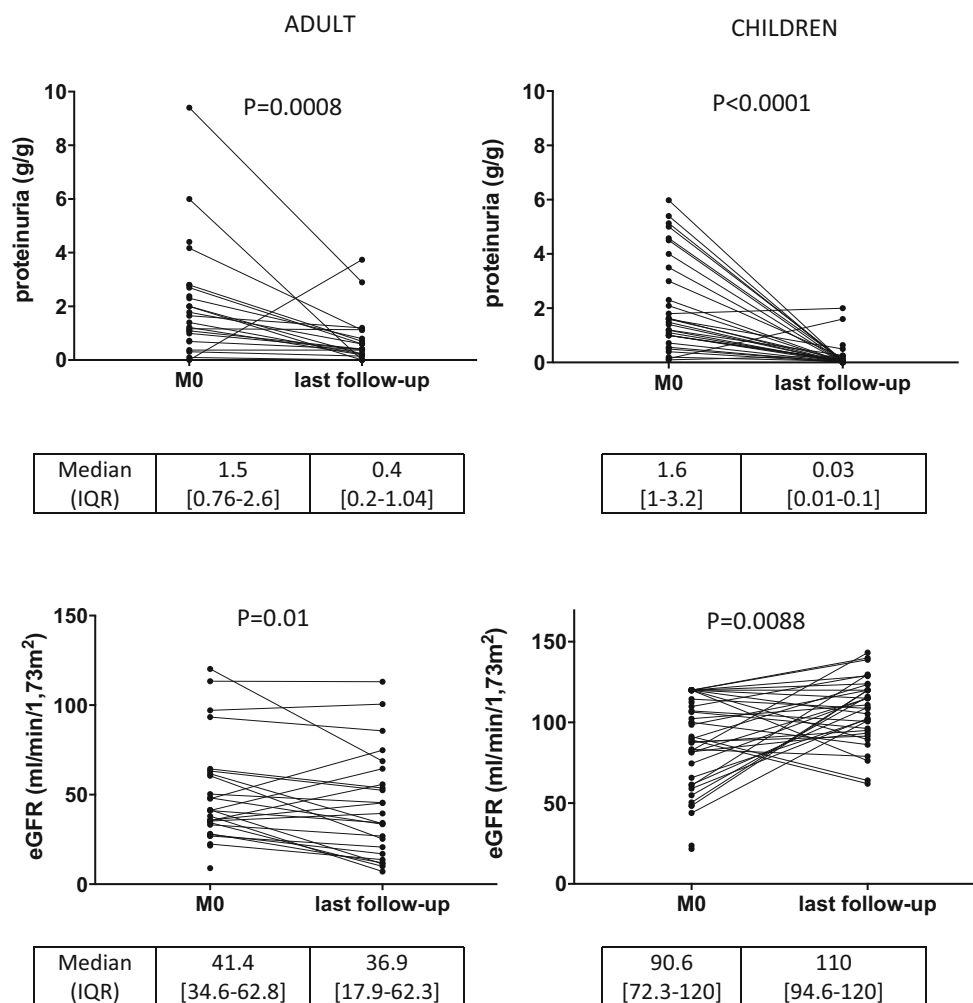


Fig. 3 Proteinuria and eGFR at the last follow-up with steroid treatment: adults versus children



features (but which may be responsive to steroids) were higher in adults compared with children. IgAN is identified as an acute glomerulonephritis in children but chronic glomerulonephritis in adults. Interestingly, it has been suggested that extracapillary hypercellularity outcome in children is quite different from adult IgAN [26]. Children and adolescents with proliferative forms of IgAN would have a significantly lower risk of reaching stage 5 CKD than adults with focal or diffuse proliferative IgAN. In the study by Haas et al., pediatric IgAN patients with diffuse extracapillary hypercellularity showed 10-year kidney survival of 63%, versus 0% in adults [18]. Nevertheless, in this study, children had normal kidney function, mild proteinuria, and focal proliferation in particular, while adults had more severe kidney dysfunction with global proliferation and globally sclerotic glomeruli and interstitial fibrosis. Also in multivariate analysis, globally sclerotic glomeruli and interstitial fibrosis are potential predictors of kidney survival. In addition, this difference is probably masked with an extended follow-up because 30% of children will eventually reach stage 5 CKD within 20 years, similar to the proportion in adult patients [10–12]. The Oxford classification

does not distinguish between fibrosis and inflamed crescents. Fibrosis crescents would be more representative of extracapillary hypercellularity in adults with IgAN than in children who manifest greater inflammation. There is still a debate about how the MEST-C score should be considered when establishing treatment for IgAN. In children with IgAN, the validation of the value of MEST-C scores is always complicated by the problem of too few end points (stage 5 CKD or 50% decline in eGFR) in small cohorts (hundreds of subjects) and median follow-ups of 5–10 years, which are insufficient to detect a functional decline in cases with early diagnosis, such as in childhood. In the Valiga cohort, kidney biopsy was performed in children with median proteinuria of 0.84 g/day/1.73 m² and mostly with normal eGFR, whereas in our French cohort kidney biopsy was performed in children with median proteinuria of 1.2 (0.3–3.2) g/g and mostly with normal eGFR [23]. In our cohort of 82 children with IgAN described previously [23], we found a higher prevalence of active lesions with a different frequency of MEST-C score distribution compared to the Valiga cohort (174 children with IgAN). In our cohort, M1, E1, S1, and C1 represented 80%,

71%, 61%, and 46%, respectively, whereas in the Valiga cohort M1, E1, S1, and C1 were 22%, 14%, 43%, and 15%, respectively, and T1–2 was 6% [27]. We found T1–2 in only 1% of kidney biopsies, thus, showing the smallest T1% of all childhood IgAN cohorts. In our cohort, the time between clinical onset and kidney biopsy was a median of less than 2 months, which explains the high detection rate of active lesions and reduction of chronic lesions compared with children from the other IgAN group. Also, criteria of kidney biopsy realization may be different in our cohort compared with the other centers. In our pediatric cohort, kidney biopsy is usually performed when proteinuria > 0.03 g/mmol. Moreover, there was a higher prevalence of severe childhood IgAN at our center. History of gross hematuria was reported in one-third of the cases, 25% presented with acute kidney injury and seven with nephrotic range proteinuria at the time of biopsy [23].

Coppo et al. reported that young adult patients with an M1 lesion have a higher risk for IgAN progression. In children, studies from Japan [28], China [29], and Sweden [30] (enrolling 161, 218 and 90 children respectively) show that according to the Oxford classification only the T1 lesion has a predictive value for progression in multivariate models adjusted for eGFR, MAP, and proteinuria at kidney biopsy. In these studies, proteinuria was significantly associated with an M1 lesion. Coppo et al. [27] also reported that M0 in children < 16 years with well-preserved eGFR (> 90 ml/min/1.73 m²) indicates a higher probability of proteinuria remission, but this does not predict IgAN progression. Last but not least, it is well known that using the MEST-C classification, the most significant lesions predictive of IgAN progression in adults are T1 and S1. We made the hypothesis that the proliferative form of IgAN, especially in children, could have sensitivity to steroid therapy, in contrast to the non-proliferative form frequent in adults. This suggests that proliferative lesions could be reversible, either spontaneously or induced by steroid treatment. Thus a slight decrease in eGFR in adults is probably related to the predominantly chronic lesions T1 and S1. In children, however, an increase in eGFR after therapy, which is associated with a highly significant decrease in proteinuria, may reflect a switch of M1 to M0. In our previous study, we also showed that podocytopathic features were predictive of kidney function decline with 6 months of follow-up [23]. In an interesting review, Trimarchi et al. similarly underlines the worse outcome of kidney function in the presence of podocytopathic features in pediatric IgAN. Immunosuppression would take time to reverse these lesions, which would need to be carefully assessed [31]. S lesions in childhood IgAN probably do not have the same significance as in adults and may be sensitive to immunosuppressive treatment.

It would be interesting to assess glomerular expression of the glucocorticoid receptor since the diminution of these receptors has been shown in IgAN patients without complete remission of their disease. In an interesting report [32], the authors have

compared patients with IgAN in complete remission versus incomplete remission after steroid treatment. Kidney biopsy showed decreased expression of the glucocorticoid receptor in patients with incomplete remission. Interestingly, groups without remission have a significantly higher proportion of S1 and T1 lesions compared with patients in remission.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines advise steroids for persistent proteinuria > 1 g/day despite 3–6 months of optimized supportive care with RASB with GFR > 50 ml/min/1.73 m² [33]. Nevertheless, the KDIGO guidelines were challenged by the outcome of a prospective randomized controlled trial. In this trial, immunosuppressive treatment (steroids ± cyclophosphamide) did not significantly improve long-term outcome in adults with IgAN at high risk of progression (i.e., with proteinuria > 0.75 g/g) [19]. There are no recommendations for IgAN treatment in children. Since children have a long life expectancy, the advice to pediatricians is to prescribe steroid treatment with RASB when proteinuria is > 0.5 g/l, eGFR deteriorates < 70 ml/min, or when glomerular inflammation is found in a kidney biopsy [34]. In this study, immunosuppressive therapy might help to reduce proteinuria in pediatric IgAN and to improve eGFR. Glomerular inflammation in children with IgAN should be considered in the same way as a potential future chronic lesion and should be treated rapidly with immunosuppression. Similarly, adult patients with endocapillary, extracapillary hypercellularity, or segmental sclerotic glomerular lesions at onset and without immunosuppressive treatment have higher eGFR deterioration [35] than patients receiving immunosuppressive therapy [4].

At last follow-up, eGFR in adults was lower than in pediatric patients ($p < 0.0001$), but proteinuria was higher ($p < 0.0001$). This highlights the fact that adults had more chronic lesions, which are less likely sensitive to steroids than in children who experience more steroid-sensitive glomerular inflammation. In adult studies, it has been shown that active lesions, such as endocapillary hypercellularity and crescents were decreased on a second biopsy after immunosuppressive therapy. The reversal was accompanied by improvement in proteinuria and hematuria [36, 37]. However, these studies found that patients with persistent proteinuria and/or impaired kidney function were those with initial chronic lesions (segmental or global glomerulosclerosis) that persisted at the second biopsy [37]. In children, similar results have been reported in the literature [38, 39]. The study by Kawasaki and Yoshikawa showed the diminution of mesangial hypercellularity, endocapillary, and extracapillary hypercellularity in the second biopsy of pediatric IgAN treated with immunosuppression.

Another purpose of this study was to highlight that IgAN may go undiagnosed until adulthood. Our hypothesis should be discussed with caution. The absence of symptoms during childhood could suggest latent disease, which can remain

undiagnosed for a long time until adulthood and may accord with a multi-hit hypothesis in the pathogenesis of IgAN [40]. The consequences of asymptomatic IgAN during childhood are not defined, and no known effect on kidney outcome has been established. Missing the diagnosis of IgAN in asymptomatic children may lead to delayed IgAN diagnosis in adulthood with CKD already established. Our pediatric cohort mostly included children with a symptomatic IgAN diagnosed during the course of routine clinical practice and not within a screening program. This underlines the importance of urinalysis screening policies to detect minor renal abnormalities during childhood, as in Japan where overall IgAN incidence is higher than elsewhere in the world [41].

This study has several limitations that should be considered. First, the data was collected retrospectively in French centers, and an important bias could be linked to missing cases not related because of incomplete data. Therapy, exposure and dosing were not recorded in detail, and the impact cannot be assessed. Given the retrospective nature of our study, there is an insufficient level of evidence in the description of the evolution of proteinuria and GFR under corticosteroid treatment in the groups, which prevents us from drawing conclusions about the efficacy of corticosteroids in children and its ineffectiveness in adults. However, IgAN is a disorder with highly heterogeneous presentations representing a significant barrier for the development of large observational studies and clinical trials, and requires a multicenter large-scale collaborative study.

Conclusions

IgAN has clinical and histological differences at time of diagnosis between children and adults. In children, IgAN is an acute glomerulonephritis unlike in adults where it generally presents as chronic glomerulonephritis. In pediatric IgAN, proteinuria seems related to glomerular hypercellularity, whereas in adults it seems associated with non-proliferative lesions. Steroids seem more effective on eGFR and proteinuria in children with glomerular hypercellularity. Onset of the disease might be asymptomatic in children and diagnosis may be delayed until adulthood.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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