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ORIGINAL ARTICLE

IgA nephropathy in children with minimal proteinuria: to biopsy or not to biopsy?

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Abstract

Background Tubulointerstitial lesions and glomerular inflammation severity have been shown to correlate with proteinuria in children with IgA nephropathy (cIgAN). However, there is a lack of data regarding severity of histopathologic findings in cIgAN in patients with minimal to absent proteinuria since kidney biopsy indications are not well defined in these cases.

Methods Twenty-eight cIgAN patients with kidney biopsy from 4 different centers in Paris (France) and Montreal (Canada) with a urine protein/creatinine ratio (UPCr) ≤ 0.03 g/mmol and a normal estimated glomerular filtration rate (eGFR > 90 ml/min/1.73 m^2) on the day of kidney biopsy prior to treatment were included.

Results Median age was 11.82 (9.32–13.45) years, and median follow-up was 4 years (2.87–6.53). At time of biopsy, median eGFR was 116 (102.3–139.7) ml/min/1.73 m^2, and median UPCr was 0.02 (0.011–0.03) g/mmol. Microscopic or macroscopic hematuria was present in 35.7% and 64.3% of cases, respectively. Kidney biopsy microscopy analysis showed mesangial (M1), endocapillary (E1), or extracapillary (C1) hypercellularity in 53.5%, 32.1%, and 7.1% of patients, respectively. Chronic histological lesions were also present: glomerulosclerosis (S1) in 42.8% and tubular atrophy/interstitial fibrosis in 7.1%. Podocytopathic features were detected in 21.4%. An ACE inhibitor or immunosuppressive therapy (IS) was prescribed in 42.8% and 21.4% of these patients respectively. One-third (35.7%) received no treatment. At last follow-up, median eGFR was 111.9 (90.47–136.1) ml/min/1.73 m^2, and median UPCr was 0.028 (0.01–0.03) g/mmol.

Conclusion cIgAN with minimal proteinuria at time of biopsy might be linked with acute and chronic glomerular lesions.

Keywords Children · IgA nephropathy · Kidney biopsy · Proteinuria

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in children after idiopathic nephrotic syndrome [1, 2]. Although childhood IgAN (cIgAN) has long been considered a benign disease, it will eventually progress to kidney failure in some children [3–5].

Some histological and clinical parameters have been identified as independent risk factors for progression towards advanced chronic kidney disease (CKD), including estimated glomerular filtration rate (eGFR) at presentation, hypertension, and proteinuria above 1 g/day [6–8].

There are new insights into the prognostic value of histological parameters. IgAN Oxford classification can predict the disease progression with a standardized pathology method forming the MEST-C score: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), interstitial fibrosis/tubular

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atrophy (T), and crescents or extracapillary hypercellularity (C) [9, 10]. The KDIGO international guidelines on glomerular diseases recommend determining the Oxford classification. However, to guide immunosuppressive treatment (IS), KDIGO recommends using proteinuria levels, but they do not recommend using the MEST-C score [11]. The impact of immunosuppressive therapy on the predictive utility of histological lesions remains undetermined. The European Validation Study of the Oxford Classification of the IgAN cohort VALIGA showed that steroid treatment blunts the predictive utility of the MEST-C score, especially for the S, C, and E lesions [10, 12]. Moreover, recent retrospective studies showed that M, S, C, and E lesions may respond to immunosuppressive treatments, unlike T lesions, which do not [13, 14]. This underlines the necessity of assessing the Oxford score to adapt IS in patients.

Most studies looking at long-term IgAN prognosis did not include patients with minimal proteinuria (< 1 g/day) at the time of diagnosis. In the study of Tan et al. [15], endocapillary and extracapillary hypercellularity were found in 45% of IgAN patients with proteinuria < 1 g/day. Guttierez et al. [16] reported 141 IgAN patients with minimal proteinuria (micro hematuria and proteinuria of 0.2 g/day) without any treatment by immunosuppressive agents. In this cohort, M1 was detected in 95 patients (67.4%), E1 in 12 patients (8.5%), and S1 in 22 patients (15.6%).

There is a lack of a specific correlation between clinical markers like proteinuria and histological lesions. IgAN with minimal proteinuria and microscopic hematuria can evolve toward a progressive disease, and few patients had hematuria disappear completely [17–20]. Furthermore, an Israeli study showed an independent correlation between isolated microscopic hematuria and the risk of kidney failure in 1,000,000 young adults monitored for military service [21].

There is a lack of data regarding the severity of histopathologic findings in cIgAN with minimal proteinuria since kidney biopsy indications are not well defined in children. The aim of our study is to describe histological lesions in cIgAN with minimal proteinuria and normal eGFR, to see if we can detect glomerular inflammation.

Methods and materials

Child IgAN patients

This retrospective multicenter international study examined cIgAN cases diagnosed between 1990 and 2021 in three pediatric nephrology departments in Paris, France (Necker Enfants Malades, Robert-Debré, and Trousseau Hospitals) and one in Montreal, Canada (Sainte-Justine Hospital). Inclusion criteria were aged < 18 years, with a new primary cIgAN diagnosed by kidney biopsy, with minimal proteinuria ≤ 0.03 g/mmol and eGFR > 90 ml/min/1.73 m^2 at the time of biopsy, and a follow-up within at least 6 months. Diagnosis of cIgAN was based on immunofluorescence staining results showing deposition of IgA in the mesangium as the co-dominant or predominant immunoglobulin deposit. Patients with Henoch–Schönlein purpura, systemic lupus erythematosus, or liver diseases were excluded.

The study was approved by the ethics committees of St. Antoine Hospital in Paris, France, and Sainte Justine in Montréal, Canada.

Clinical data set

For each patient, the following clinical and biological characteristics were collected at the time of biopsy and at last follow-up: sex, age, height, weight, systolic and diastolic blood pressure, presence of macroscopic hematuria, time from onset to kidney biopsy, serum albumin, serum creatinine (sCreat, [µmol/l]), eGFR, and urine protein-to-creatinine ratio (UPCr [g/mmol]). Proteinuria was also measured at the first check-up prior to kidney biopsy. The Schwartz equation was used to calculate eGFR: creatinine clearance (ml/min/1.73 m^2) = $K \times L$/ sCreat, where L is body length (cm) and $K = 41.3$ [22, 23]. Minimal to no proteinuria was defined as UPCr ≤ 0.03 g/mmol. Microscopic hematuria was defined as more than five erythrocytes per field of view, and macroscopic hematuria was characterized by the presence of gross hematuria. History of macroscopic hematuria was defined as the presence at least one episode of gross hematuria. Kidney failure was characterized as an eGFR below 15 ml/min/1.73 m^2.

Histopathology

The kidney biopsy samples were re-classified by two nephropathologists in France (Robert Debré and Necker Hospital) and one in Canada (Sainte Justine Hospital) according to the Oxford classification MEST-C score: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and interstitial fibrosis/tubular atrophy (T) crescents or extracapillary hypercellularity (C). Podocytopathies (P) were scored as absent (P0) or present (P1) using the Columbia Working Group definition [24].

Statistical analysis

For the description of continuous and categorical variables, frequencies and median (interquartile range (IQR)) values were used. Fisher's and Mann–Whitney tests were employed to compare categorical and continuous variables, respectively. A p value ($p < 0.05$) was considered statistically significant. Kidney survival analysis with eGFR < 90 ml/min/1.73 m^2 was done using Kaplan–Meier survival.

Statistical analyses were done with GraphPad Prism version 8 (GraphPad Software).

Results

Clinical description

The study sample included 28 children (25 males) with suspected IgAN who had proteinuria ≤ 0.03 g/mmol and eGFR > 90 ml/min/1.73 m^2 at the time of biopsy. 92.8% had at least one isolated history of macroscopic hematuria without skin, bowel, or arthritis manifestation which led to a medical consultation with a median proteinuria of 0.035 (0.01–0.11). Blood pressure was normal. Median age was 11.82 (9.32–13.45) years. Median eGFR was 116 (102.3–139.7) ml/min/1.73 m^2, and median UPCr was 0.02 (0.011–0.03) g/mmol. Albumin levels were normal in all patients, with a median of 40 (37.7–42.0) g/l. Macroscopic hematuria was detected in 64.3% of patients, and 35.7% (10/28) had it at the time of the kidney biopsy. Delay between first symptoms and kidney biopsy was 4.25 months (1.88–10.75) (Table 1).

Kidney biopsy

cIgAN with minimal proteinuria was associated with mesangial proliferation (M1) in 53.5% (15/28) (M1), endocapillary proliferation (E1) in 32.1% (9/28), glomerulosclerosis (S1) in 42.8% (12/28), tubular atrophy/interstitial fibrosis (T1) in 7.1% (2/28), and extracapillary proliferation (C1) in 7.1% (2/28) of the patients. Focal segmental glomerulosclerosis (FSGS) with P1 podocytopathic features was present in 21.4%, and 21.4% (6/28) had M1, E1, S1, and T0 in the same biopsy (Table 2 and Fig. 1).

Table 1 Clinical and biological characteristics cIgAN with minimal proteinuria

Variables[a]	*N* = 28
Proteinuria at the first clinical visit (g/mmol)	0.035 (0.01–0.11)
Macroscopic hematuria history	92.8%
At the time of kidney biopsy	
Time between onset and kidney biopsy (months)	4.25 (1.88–10.75)
Age (years)	11.82 (9.325–13.45)
Male	25; 89%
eGFR (ml/min/1.73 m^2)	116 (102.3–139.7)
Serum albumin (g/l)	40 (37.7–42.0)
Proteinuria (g/mmol)	0.02 (0.011–0.03)
Microscopic hematuria	35.7%
Macroscopic hematuria	64.3%
Treatment after kidney biopsy	
ACE or ARBs alone	12 (42.8%)
Immunosupressive therapy and ACE	6 (21.4%)
No treatment	10 (35.7%)

[a]For quantitative variables, values are expressed. For qualitative variables, values are expressed as *n* (%). *eGFR*, estimated glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker

Treatment

Six patients (21.4%) received immunosuppressive (IS) treatment (corticosteroids) and renin angiotensin system blocker (RASB) treatment after kidney biopsy. Of the six patients who received IS treatment, all had M1, two had E1, one had C2, two had P1, three had S1, and none had T1 detected at

Table 2 Histological characteristics of cIgAN with minimal proteinuria

Pathological findings	*N* = 28
M1	15 (53.5%)
E1	9 (32.1%)
C1	2 (7.1%)
S1	12 (42.8%)
T1	2 (7.1%)
P1	6 (21.4%)

M1, presence of mesangial hypercellularity; *E1*, presence of endocapillary hypercellularity; *C1*, presence of extracapillary proliferation; *S1*, presence of glomerulosclerosis; *T1*, presence of tubular atrophy; *P1*, presence of podocytopathic features

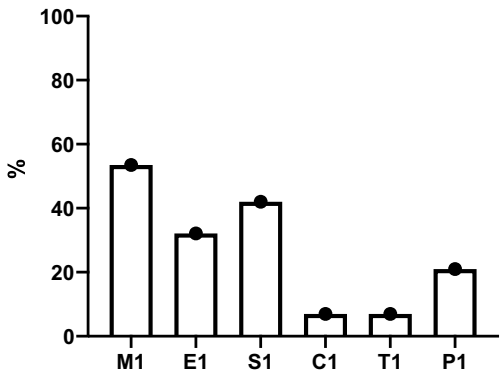

Fig. 1 Histological characteristics of cIgAN with minimal proteinuria. M1, presence of mesangial hypercellularity; E1, presence of endocapillary hypercellularity; C1, presence of extracapillary proliferation; S1, presence of glomerulosclerosis; T1, presence of tubular atrophy; P1, presence of podocytopathic features

Table 3 Biological characteristics cIgAN with minimal proteinuria at last follow-up

Variables	$N=28$
Follow-up (year)	4.47 (2.87–6.53)
Macroscopic hematuria history	92.8%
eGFR (ml/min/1.73 m^2)	111.9 (90.47–136.1)
Serum albumin (g/l)	40 (37.70–42)
Proteinuria (g/mmol)	0.015 (0.01–0.03)
eGFR < 90 ml/min/1.73 m^2	6; 21.4%

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

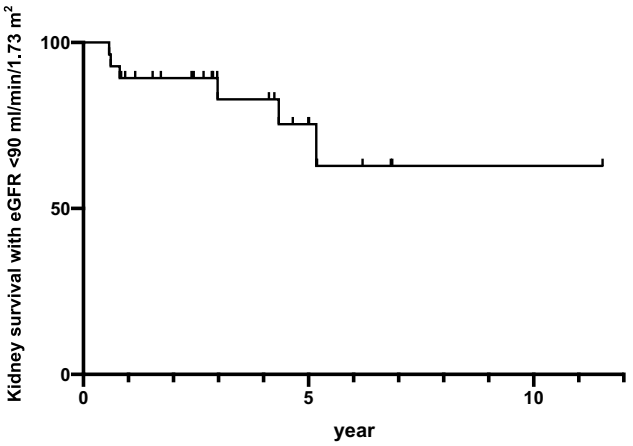

Fig. 2 CKD in cIgAN with minimal proteinuria

the kidney biopsy. In addition, one patient received methylprednisolone pulses with one cyclophosphamide pulse due to the presence of excessive extracapillary hypercellularity, 42.8% (12/28) patients were on RASB treatment only, and 35.7% (10/28) patients remained untreated. No patient underwent tonsillectomy (Table 1).

Follow-up

Median follow-up was 4.47 (2.87–6.53) years. At last follow-up, one patient suffered kidney failure. Median eGFR was 111.9 (90.47–136.1) ml/min/1.73 m^2 and median UPCr 0.015 (0.01–0.03) g/mmol. Six patients (21.4%) had an eGFR < 90 ml/min/1.73 m^2 (Table 3 and Fig. 2).

We compared patients with eGFR < 90 ml/min/1.73 m^2 and patients with eGFR > 90 ml/min/1.73 m^2 at the last follow-up. In the former group, the median eGFR was 87.32 ml/min/1.73 m^2 (59.17–89.64), median proteinuria was 0.02 (0.01–0.07), and three patients had proteinuria > 0.03 g/mmol. More active E1 and C1 lesions were observed in the low eGFR group (M1 83.3% vs. 45.4% $p=0.09$; E1 83.3% vs. 18.1%, $p=0.002$; C1 33.3% vs. 0%, $p=0.005$, respectively) along with more podocytopathic features (P1 50% vs. 13.6%, $p=0.05$). The median follow-up was not significantly different: 4.72 vs. 4.08 years ($p=0.24$). Moreover, for the low eGFR group, the delay for kidney biopsy was longer (13.42 vs. 3.12 months, $p=0.01$), patients received more IS (66.6% vs. 13.6%), and proteinuria was not different (UPCr 0.025 vs. 0.01 g/mmol, $p=0.19$) (Table 4).

Discussion

This study suggests that cIgAN presenting with hematuria and minimal proteinuria could be associated with active and chronic histological lesions. Indeed, proliferative lesions (E1 and C1) were found in 37.3% of these patients. This lack of correlation between the clinical presentation and the biopsy suggests that histology may help predict patients' risk of kidney failure and guide the therapeutic management of these patients.

There is an ongoing debate on how to include histological findings (Oxford classification) in treatment decision-making for IgAN. In adults with suspected IgAN, a kidney biopsy is not recommended in case of isolated microscopic hematuria, due to the lack of evidence supporting the benefit of immunosuppression in individuals with IgAN without proteinuria and the reported increase in infectious complications in adults with IgAN treated with glucosteroids in randomized controlled trials (RCTs). In such cases, therapy consists only of conservative measures including the treatment of hypertension with renin angiotensin system blockade, which would be applicable to any patients with CKD and without proteinuria, regardless of pathology.

The international guidelines from KDIGO on glomerular diseases do not recommend using Oxford classification for IS therapy indication, but the KDIGO guidance recommends the use of proteinuria for guiding the use of IS [11]. They base this decision solely on the level of proteinuria and baseline eGFR if there are no contraindications to corticosteroids [11]. Only two RCTs have included a priori hypotheses regarding the impact of histological findings on the benefits of immunosuppression, but a considerable delay occurred between the kidney biopsy and treatment allocation, which did not permit the question to be answered in either trial [25, 26]. Nevertheless, multiple large observational studies have shown that immunosuppression modifies the association between histological lesions and renal outcomes [10, 12]. This is supported by recent retrospective studies, including our own, demonstrating that M, S, C, and E lesions respond to immunosuppressive treatment, but T lesions do not [13, 14].

Compared to adults, IgAN in children is an acute glomerulonephritis frequently without chronic lesions. This is reflected by higher frequencies of acute nephritic/nephrotic syndrome and acute kidney injury at onset [27].

Table 4 Comparison at last follow-up of patients with eGFR < 90 ml/min/1.73 m^2 and > 90 ml/min/1.73 m^2

Variables[a]	eGFR < 90 ml (6)	eGFR > 90 (22)	*p*
Mean age	11.83 years ± 2.37	10.87 ± 4.1	*p* = 0.93
First proteinuira before kidney biopsy (g/mmol)	0.055 (0.01–0.03)	0.035 (0.01–0.03)	*p* = 0.77
Macroscopic hematuria history	6; (100%)	20 (90.9%)	*p* =
Proteinuira (g/mmol)	0.02 (0.01–0.07)	0.02 (0.01–0.03)	*p* = 0.88
Macroscopic hematuria	3; (50%)	16; (72.72%)	*p* = 0.29
Microscopic hematuria	3; (50%)	6; (27.27%)	*p* = 0.29
Time between onset and kidney biopsy (months)	13.42 (6.8–24.8)	3.12 (1.68–6.95)	*p* = 0.01
Pathological findings			
M1	5; (83.3%)	10; (45.4%)	*p* = 0.09
E1	5; (83.3%)	4; (18.1%)	*p* = 0.002
C1	2; (33.3%)	0; (0%)	*p* = 0.005
S1	2; (33.3%)	10; (45.45%)	*p* = 0.59
T1	0; (0%)	2; (9%)	*p* = 0.44
P1	3; (50%)	3; (13.6%)	*p* = 0.05
Treatment			
IS + RASB	3; (50%)	3; (13.6%)	*p* = 0.05
RASB alone	1; (16.6%)	11; (50%)	*p* = 0.34
No treatment	2; (33.3%)	8; (36.36%)	*p* = 0.88
Follow-up (years)	4.72; (3.87–10.49)	4.08; (2.68–6.35)	*p* = 0.24
Proteinuria last follow up (g/mmol)	0.025; (0.01–0.077)	0.01; (0.01–0.02)	*p* = 0.19

M1, presence of mesangial hypercellularity; *E1*, presence of endocapillary hypercellularity; *C1*, presence of extracapillary proliferation; *S1*, presence of glomerulosclerosis; *T1*, presence of tubular atrophy; *P1*, presence of podocytopathic features; *IS*, immunosupressive treatment; *RASB*, renin angiotensin system blocker

[a]For quantitative variables, values are expressed as median (interquartile range IQR). For qualitative variables, values are expressed as *n* (%)

Proteinuria can reflect both the presence of glomerular inflammation (M, E, and C lesions) and the presence of chronic lesions (especially glomerulosclerosis, S lesions). Inflammatory lesions are more prevalent in children and may account for the higher sensitivity to corticosteroids reported in this population. In cIgAN, proteinuria is associated with M1, E1, and C1 as opposed to S1, P1, and T1 in adults, and cIgAN has a higher corticosensibility than adult IgAN [27]. However, no pediatric RCTs exist to demonstrate that these lesions respond well to therapy and therefore do not impact kidney function in the short term. Kawasaki et al. also reported improved glomerular inflammation with steroid therapy (mesangial, endocapillary, and extracapillary hypercellularity), including a lower proportion of segmental sclerosis and glomerulosclerosis at the second kidney biopsy. Moreover, Coppo et al., using the VALIGA cohort, reported that young adult patients with M1 have a higher risk for IgAN progression, suggesting that M1 is not benign, and that histology should be considered for treatment indication [28].

Ethnicity has also been shown to be a factor in IgAN severity and should be included in kidney biopsy indications. The prevalence of kidney failure in patients with IgAN is higher in patients from Asia than in Caucasians. In Pacific-Asian origin patients, more glomerular inflammation and more tubular atrophy were observed than in the European VALIGA cohort [29].

In the present study, significant pathological features were found in cIgAN patients with minimal proteinuria, as was described in other adult IgAN cohorts with minimal proteinuria [15, 16].

The KDIGO guidelines do not recommend a specific proteinuria threshold to perform biopsies in children. Some centers do biopsy child patients with minimal proteinuria to confirm the diagnosis. The purpose and the risk of the biopsy are fully explained to the patients and their caregivers who give their written consent.

Even though eGFR at last follow-up was normal in 81.6% of the patients, we found pathological evidence of glomerular inflammation in 38.2% of patients, endocapillary proliferation in 31.2%, and extracapillary proliferation in 7% of them. These lesions are known to be independent predictors of eGFR decline without any treatment [30]. Given the strong indication bias for the use of IS (patients with more severe lesions are more likely to be treated with IS) and the small sample size, our study does not allow us to draw any firm conclusions about the potential benefit of IS treatment in our patients. Also, other factors could explain a good outcome, including RASB treatment in 42.8% and also a quick follow up.

Moreover, in cIgAN patients with an eGFR < 90 ml/min/1.73 m^2, more E1, C1, and P1 were observed at the first kidney biopsy, and the time between clinical onset and kidney biopsy was longer, explaining the high detection rate of active lesions compared to cIgAN with normal eGFR at last follow-up. Podocytopathic features are correlated with a worse outcome in adults and cIgAN [31–33]. To reverse these histological lesions, immunosuppressive treatment would take time, which would need to be carefully documented [31–33]. Unfortunately, we do not have finer data granularity for each patient's care trajectory. However, our results suggest that severe histological lesions are likely a marker of a more active disease overall, which may lead to decreased eGFR in some patients.

There is an ongoing debate in kidney biopsy timing: whether to perform the biopsy early to detect rapidly growing active lesions and avoid fibrosis [34] or to wait until the proteinuria level is lower. cIgAN KDIGO guidelines recommend performing kidney biopsies at presentation of symptoms (hematuria, proteinuria, normal C3) in order to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis, but they do not suggest a timeframe [35]. In our study, the average delay between the first symptoms and the first kidney biopsy was 4.2 months. This led to the detection of acute kidney histologic lesions, which allows us to think that this delay would be a good recommendation for the first kidney biopsy.

Kidney biopsies present minimal risk in pediatric patients when performed in a specialized center. Perinephric hematomas can occur after kidney biopsy, but the proportion of patients requiring additional intervention or blood transfusion due to the kidney biopsy in pediatric patients is rare when clear risk factors have been identified (platelet count, and hemodialysis) [36].

Using kidney biopsy results instead of proteinuria level would allow us to distinguish between active and chronic lesions, which would help us to define those patients who would benefit from IS treatment and those who would benefit only from renoprotective treatment (RASB treatment, sodium-glucose co-transporter-2 inhibitors (SLGT2), etc.), while avoiding unnecessary IS side effects. Currently, the optimal timing to perform a kidney biopsy is unclear.

We need RCTs to validate an association between inflammatory glomerular lesions and a greater response to IS treatment, as opposed to chronic tubulointerstitial findings, as was described in a recent retrospective study [13, 14].

Our study has some limitations. First, data were retrospectively collected in French and Canadian centers, resulting in some missing data. Since it is a rare disease, the cohort sample size was small. Time of treatment exposure and dosing were not recorded in detail, and their impact cannot be assessed.

Conclusion

Active histological lesions are frequent in children with IgAN despite benign clinical manifestations. Moreover, these histological lesions seem to be associated with a higher risk of eGFR decline. Therapeutic strategies based on histology are likely to increase the number of patients treated, and further studies are needed to assess whether such a strategy improves kidney outcomes in cIgAN.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-023-06121-7.

Data availability Data are secured in a computer server in Sainte Justine's research center.

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