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Renal Function Adaptation up to the Fifth Decade After Treatment of Children With Unilateral Renal Tumor: A Cross-Sectional and Longitudinal Study

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Background. Mild-to-moderate renal function loss may be an independent risk factor for cardiovascular disease and overall mortality. As in adults with renal carcinoma nephrectomy is associated with an high risk for moderate renal function loss, we aimed to assess the renal function adaptation over a long period of time in children with unilateral renal tumor (URT). ***Procedure.*** Seventy-two children who underwent surgery for URT were enrolled in this study. Glomerular filtration rate was estimated (eGFR) with the Modification of Diet in Renal Study or the Schwartz equation, as appropriate for the age. ***Results.*** Twelve patients treated by nephron-sparing surgery (Group A) and 42 treated by nephrectomy (Group B) had an age between 2 and 30 years; 18 patients treated by nephrectomy had an age between 33 and 51 years (Group C). At cross-sectional follow-up 8% patients of Group A, 42% of Group B and 78% of Group C presented a mild-to-moderate renal function. The longitudinal data stratified by post-operative intervals showed that patients of Group C presented a significant progressive decrease in mean ± standard deviation eGFR (88.1 ± 22.6 during the third decade after surgery vs. 66.6 ± 15.6 ml/min/1.73 m^2 during the fifth decade after surgery; $P = 0.02$). The longitudinal data stratified by age showed that patients with an age between 45 and 54 years presented a mean eGFR significantly lower than that expected for the physiological renal function decline with aging ($P = 0.001$). ***Conclusion.*** Aging is associated with a mild-to-moderate renal function loss in many adult patients following nephrectomy during childhood for URT. Pediatr Blood Cancer 2013;60:1534–1538.

Key words: mesoblastic nephroma; nephrectomy; nephron-sparing surgery; renal carcinoma; renal function; Wilms tumor

INTRODUCTION

Adults with unilateral renal carcinoma undergoing nephrectomy often develop a moderate renal function loss, which may be an independent risk factor for cardiovascular disease and increased overall mortality. Therefore, in patients with small renal cell carcinoma nephron-sparing surgery (NSS) is considered the treatment of choice [1].

In children with Wilms tumor without syndromes predisposing to a contralateral renal tumor, NSS is not recommended mainly because the incidence of end stage renal disease after nephrectomy is very low. The cumulative incidence of renal failure was 0.6% for 5,347 patients with unilateral Wilms tumor at 20 years after diagnosis [2]. Actually, Robitaille et al. reported the results of a cross-sectional study of renal function in children undergoing unilateral nephrectomy for oncological and non-oncological indications. The conclusion was that, on average, renal function, after an initial increase up to 75% of that of healthy controls with two kidneys, remains stable for 30 years after surgery [3].

A longitudinal study on renal function adaptation after nephrectomy or NSS in children with unilateral renal tumor (URT) has recently challenged the concept that ablation of 50% of renal mass is followed by a satisfactory renal function adaptation [4]. At a mean post-operative follow-up of 10 years, 50% of the patients undergoing nephrectomy and those undergoing NSS presented a significant increase in estimate glomerular filtration rate (eGFR) reaching values similar to those of subjects with two healthy kidneys. The other half patients undergoing nephrectomy presented a negligible increase in eGFR and developed a mild renal function loss. Main limitations of the letter study included the small sample size and the relatively short follow-up. Therefore, the present study was designed to assess the renal function adaptation over a longer post-operative follow-up and in a larger cohort of children undergoing treatment for URT.

METHODS

The operating room books of our academic pediatric surgery unit enabled us to create a file of the children who had undergone surgery for a URT. During the last 50 years (1962–2011) 99 children were operated by three different surgeons. The review of available hospital records allowed us to update the database we used in previous studies [5,6]. We extracted from the hospital records the following data: sex, age at surgery, age at last follow-up, serum creatinine values with age, and height at time of each available measurement, histological type and stage of different primary renal tumor, and type of adjuvant therapy.

Three patients with synchronous bilateral Wilms tumor were excluded. Twenty-four patients, including 21 who died, had insufficient data to evaluate the renal function. Seventy-two patients with URT were enrolled in the present study. Sixty patients underwent a nephrectomy. In 1992, we began to consider NSS in children with URT and normal contralateral kidney. Therefore, 12 patients with unilateral Wilms tumor or benign renal tumor underwent enucleation or partial nephrectomy performed without hilar control or cooling; local ischemia was obtained using digital parenchymal compression.

The new address of many patients was traced through the register of births of the town where they were born. All surviving patients or their parents received a letter or a telephone call to explain the reasons of present study and were invited to attend a special follow-up for a clinical and laboratory evaluation. In addition they were asked to provide all available post-surgery results of blood and urine examinations.

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Conflict of interest: Nothing to declare.

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The main outcome investigated was the change of renal function over a long post-operative time. The eGFR was regarded as the best measure of renal function. In patients ≤17-year-old eGFR was calculated using the update bedside Schwartz equation, GFR = 0.413 × height (cm)/serum creatinine (mg/dl) [7]. In patients who were 18 years or older, eGFR was calculated with the abbreviated Modification of Diet in Renal Disease Study equation, GFR = $32.788 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ for female and/or × 1.212 for black patients [8].

Serum creatinine (over 1,675 measurements) was determined with a colorimetric assay by autoanalyzer. All serum creatinine values were within normal limits. Different measurements of serum creatinine for each year were averaged. To have a significant sample size, sequential measurements of eGFR were arbitrarily analyzed by 10 post-operative intervals groups. As widely accepted, decreased renal function was classified as mild (eGFR = 60–89 ml/min/1.73 m^2) or moderate (eGFR = 30–59 ml/min/1.73 m^2).

The differences between the two groups for every variable of interest were evaluated by the parametric *t*-test (in case of homoscedasticity) or the parametric Welch test (in case of missed homoscedasticity). The nonparametric Wilcoxon–Mann–Whitney was used to evaluate the differences between the same groups for every variable of interest at different time of follow-up. Fisher's exact test was used to assess the statistical significance of the relationship between categorical variables. The longitudinal changes in eGFR were studied through the linear regression analysis. The hypothesis of no difference between two categories of observations in the population was rejected only if the *P* level reported for parametric and nonparametric tests was equal to or smaller than 0.05 for both tests. In the text, values are reported as mean ± SD or as mean ± SEM. Statistical analysis was implemented using Spss13.0 statistical software. This study was approved by the appropriate institutional review board: informed consent was obtained from the patients or the parents, as appropriate.

RESULTS

Cross-sectional analysis of eGFR versus age at the time of last investigation showed that patients who underwent nephrectomy presented a trend towards a progressive decline in eGFR with aging (Fig. 1). Conversely, patients who underwent NSS presented a trend to an increase in eGFR up to the third decade of life.

Table I shows that at last eGFR investigation the 12 patients under the age of 25 years who underwent NSS (Group A) in comparison with 42 patients under the age of 30 years who underwent nephrectomy (Group B) presented a significant higher mean ± SD eGFR (109.8 ± 18.4 vs. 95.1 ± 18.5 ml/min/1.73 m^2; $P = 0.02$). The two groups did not show significant differences in male/female distribution, age at surgery, age at follow-up, and length of post-operative interval. Group A patients were all Stages I and II and all disease-free survivors. Eleven Group B patients died (two for reason not related to tumor progression). Group B patients in comparison with Group A included a significant higher number of patients with mild renal function loss (43% vs. 8%; $P = 0.03$). The 18 patients with an age between 33 and 51 years who underwent nephrectomy (Group C), in comparison with Group B presented a very significant decrease in mean ± SD eGFR (76.1 ± 16.3 vs. 95.1 ± 18.5 ml/min/1.73 m^2; $P = <0.001$). Group C patients in comparison with Group B patients presented a significant increase in the number of patients with mild-to-moderate renal function loss (78% vs. 43%; $P = 0.02$). Only one 51-year-old diabetic patient required at the age of 46 years short-term hemodialysis. The acute renal failure was associated with a Leriche syndrome complicating surgery for post-radiation lumbar scoliosis. At last follow-up she has an eGFR = 46 ml/min/1.73 m^2.

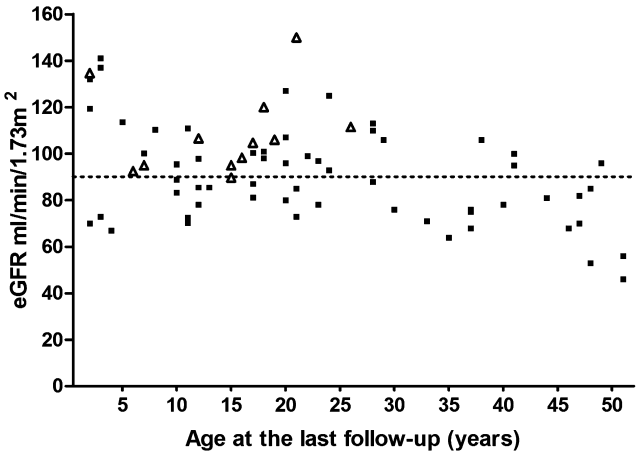

Fig. 1. Cross sectional age differences in individual estimated glomerular filtration rate (eGFR) at the time of the last investigation of 60 patients undergoing nephrectomy (■) and 12 patients undergoing nephron-sparing surgery (△). The line indicates the lower value in eGFR of subjects with two healthy kidneys.

No significant differences in mean eGFR were found between 9 patients treated only by nephrectomy and 18 patients treated by nephrectomy associated with 2 drugs chemotherapy (83.73 ± 12.33 vs. 93.51 ± 18.53; $P = 0.6$). Similarly, no significant differences were found in mean eGFR between 33 patients treated by nephrectomy associated with 3 drugs chemotherapy and/or radiotherapy and the 18 patients treated by nephrectomy associated with 2 drugs chemotherapy (90.07 ± 22.81 vs. 93.51 ± 18.53; $P = 0.09$).

The results of longitudinal analyses of eGFR changes in relation to post-operative intervals confirmed the cross-sectional trends (Fig. 2). Patients were censored at the time of last investigation before death. At diagnosis, eGFR was available in 52 patients of Groups A and B. Thirty of these (59%) had a pre-existing mild renal function loss. Before surgery no significant differences were found between mean eGFR of Groups A and B patients. At the second decade after surgery, Group A patients showed a significant increase in mean ± SD eGFR from 91.2 ± 15.7 ml/min/1.73 m^2 to 110.3 ± 18.8 ml/min/1.73 m^2 ($P = 0.03$). Conversely, at a similar post-operative follow-up, Group B patients showed a non-significant increase in mean ± SD eGFR from 85.2 ± 33.7 ml/min/1.73 m^2 to 91.2 ± 15.7 ml/min/1.73 m^2 ($P = 0.74$). After surgery the mean eGFR of Group A was significantly higher than of Group B patients ($P = 0.01$). Group C patients showed a significant progressive decrease in mean ± SD from 88.1 ± 22.6 during the third decade after surgery to 66.6 ± 15.6 ml/min/1.73 m^2 during the fifth decade after surgery (slope = −1.28 to −0.47; $P = 0.02$) (Fig. 2). During the fifth decade after surgery, 7 of 8 patients presented an eGFR between 86 and 46 ml/min/1.73 m^2.

To facilitate comparison with data in normal subjects, sequential measurements of eGFR were stratified by the same age interval

TABLE I. Characteristics, Oncological Diagnosis, and Estimated Glomerular Filtration Rate (eGFR) At Last Postoperative Follow-Up in 72 Patients Who Underwent Ablative Surgery for Unilateral Renal Tumor

	Group A	Group B	Group C
Male/female	4/8	18/24	7/11
Age at surgery (years) (mean±SD)	3.9±3.2	3.6±2.9	4.47±3.14
Age at last follow-up (years) (mean±SD)	15.18±6.6	15.8±8.0	42.7± 5.7
Post-op follow-up (years) (mean±SD)	11.7±6.5	11.38±7.8	38.44±4.9
No. of deaths	0	11	0
eGFR (ml/min/1.73m^2)	109.8±18.4	95.1±18.5°	76.1±16.3*
No. of patients with eGFR<90ml/min/1.73m^2	1	18$^{\infty}$	14^{+}
Mesoblastic nephroma	—	2	1
Wilms tumor	10	32	17
Cystic nephroma	1	3	—
Oncocitoma	1	—	—
Renal cell carcinoma	—	3	—
Clear cells sarcoma	—	1	—
Rabdoid tumor	—	1	—
Stage			
I–II	12	27	12
III–IV	—	15	6
Surgery only	3	7	2
Two drugs	4	14	4
Three drugs/radiotherapy	5	21	12
Preoperative chemotherapy	12	33	4

Group A includes 12 patients ≤30 years old who underwent nephron-sparing surgery; Group B includes 42 patients ≤30 years old who underwent nephrectomy; Group C includes 18 patients ≥30 years old who underwent nephrectomy. $^{\circ}$Group A versus Group B: $P = 0.02$; *Group B versus Group C: $P < 0.001$; $^{\infty}$Group A versus Group B: $P = 0.03$; $^{+}$Group B versus Group C: $P = 0.02$.

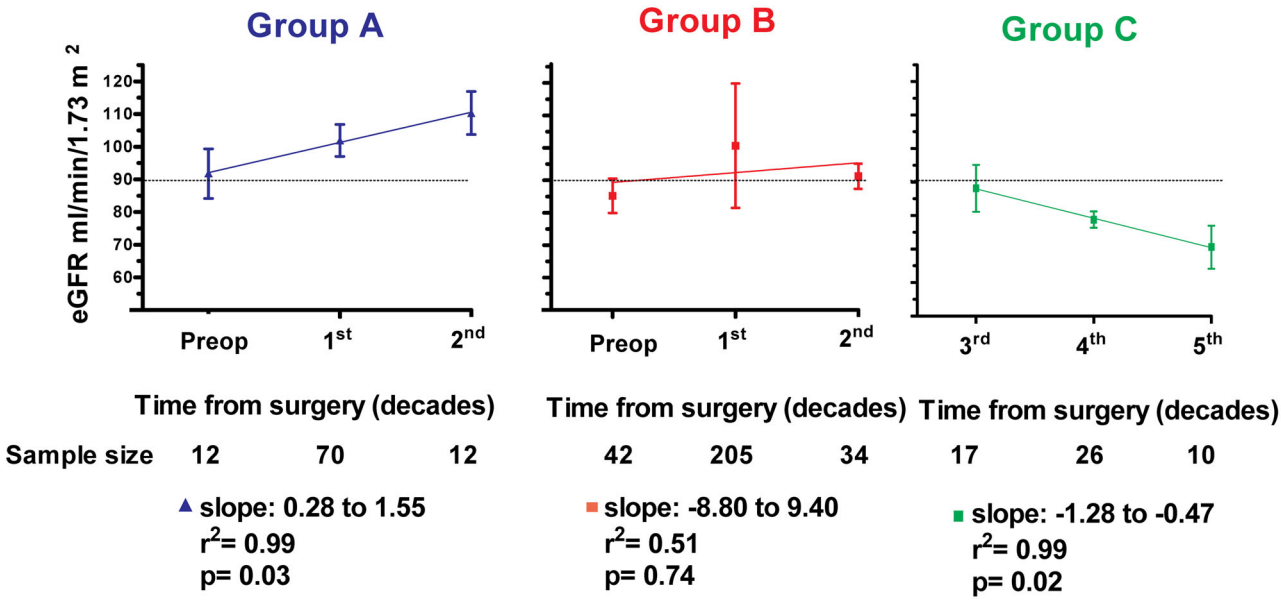

Fig. 2. Longitudinal regression analysis of estimated glomerular filtration rate (eGFR) versus post-operative intervals in 72 patients who underwent ablative renal surgery for unilateral renal tumor. Note that during the second decade after surgery the 12 patients who underwent nephron-sparing surgery (Group A) presented a significant increase in eGFR, whereas the 42 patients who underwent nephrectomy (Group B) presented a negligible increase in eGFR. During the fifth decade after surgery, the 18 patients who underwent nephrectomy (Group C) presented a significant decrease in eGFR.

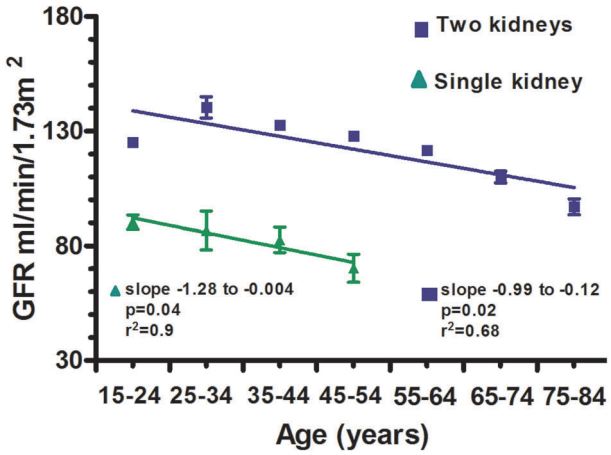

Fig. 3. Comparison of longitudinal age changes in glomerular filtration rate (eGFR) of subjects with two healthy kidneys (■) (data from reference 9) and eGFR of patients (△) following nephrectomy for unilateral renal tumor during childhood. Values are mean ± SEM.

groups reported in normal subjects [9]. The longitudinal analysis of eGFR in relation to age showed that patients undergoing nephrectomy experience a progressive decrease of renal function that parallels the physiological decline of renal function in subjects with two healthy kidneys (Fig. 3). However, the mean ± SEM value of eGFR in patients with an age between 45 and 54 years was significantly lower than that of normal subjects (70.28 ± 6.1 vs. 128.1 ± 1.6; $P = 0.001$).

DISCUSSION

In the present study, we found that more than 50% of patients presented a pre-existing decreased renal function, a prevalence similar to that found in our previous report on a smaller cohort of children with URT [4]. The exact mechanism of this association is not known. In adults with renal cell carcinoma it is not clear if the pre-existing decreased renal function is a direct consequence of renal neoplasia or the result of medical co-morbidities causing changes that predispose to malignant transformation [10]. Whatever the mechanism of this association can be, there is a distinct difference in baseline renal function between kidney tumor patients and kidney donors who are screened for decreased renal function and other medical co-morbidities [10].

In the present cohort of children with URT, we found that about 43% of patients under the age of 30 years presented after nephrectomy a mild renal function loss. This prevalence is similar to that reported in our previous report on a smaller cohort of patients [4]. The mild renal function loss is probably the result of inadequate renal function compensation after nephrectomy. Our previous conclusion was that this subset of patients would probably benefit of a nephron-sparing approach. The novel finding of the present cross-sectional and longitudinal study is that patients undergoing nephrectomy after the age of 30 years presented an increasing number of patients with a $\leq$90 ml/min/1.73 m^2 GFR. During the fifth decade after surgery, 87.5% of the patients presented a mild-to-moderate renal function loss.

The direct association we found between aging and increasing number of patients with decreased renal function after nephrectomy for URT during childhood is not surprising. In an unselected group of 36 adult patients born with unilateral renal agenesis or undergoing nephrectomy in childhood because of hydronephrosis, Wikstad et al. [11] found that GFR declined significantly in the group with a follow-up time of 26–40 years in comparison with the group with a follow-up time of 7–15 years. The results of another similar cross-sectional study supported the concept that adult patients undergoing unilateral nephrectomy in childhood present after the age of 30 years a significant and progressive decline of renal function. Data were obtained from 111 patients who underwent nephrectomy for unilateral renal disease including 14 children with Wilms tumor. Separate analysis of the last group of patients showed no significant differences with the non-oncological patients [12]. Accordingly, in the present study, we found no significant differences in post-nephrectomy renal function adaptation between patients who did or did not have chemotherapy and/or radiotherapy.

Cross-sectional study design do not necessarily reflects true age changes since the older subjects may represent selected survivors. The limitation of cross-sectional studies prompted the longitudinal design of present study in which serial measurements of eGFR were made in the same subjects over time. The present longitudinal age changes in eGFR approximated the cross-sectional age differences. During the second decade after surgery the mean ± SD eGFR of patients undergoing nephrectomy was significantly lower than that of patients undergoing NSS ($P = 0.01$) who presented a mean eGFR which lie within the normal range (Fig. 2). Therefore, it is unlikely that at longer follow-up patients undergoing NSS may present changes in eGFR different from age-related changes seen in individuals with two healthy kidneys. Conversely, in our opinion, the lower values in eGFR following nephrectomy associated with physiological age-related decline of GFR, may be responsible, at least in part, for the present high prevalence of patients with decreased renal function after the age of 30 years. In addition, patients undergoing nephrectomy will probably experience at a longer follow-up a further progressive decrease in eGFR as the renal function physiologically declines up to the age of more than 80 years (Fig. 3). Whether hyperfiltration may contribute to the renal function deterioration remains to be investigated.

The negative correlation between aging and renal function loss in adults who underwent unilateral nephrectomy during childhood has been considered uneventful because the low rate of decline may allow avoiding renal failure up to the age of 80 years [12].

During the last 10 years evidence is accumulating that not only renal failure but also mild-to-moderate renal function loss may represents an independent risk factor for cardiovascular disease and overall mortality [13–16]. The corollary is that to save as much as possible of renal parenchyma without compromising the oncological outcome should be the goal of surgical treatment not only of adults but also of children with URT. However, in children further studies are required to assess if NSS is oncologically safe.

Our study has several limitations. First, the patients analyzed represent a retrospective single-institution experience and no data were available to evaluate the renal function in about ¼ of the patients. In addition the equations we used to estimate GFR are considered reasonably accurate at eGFR of <60/ml/min/1.73 m^2, whereas these equations underestimate eGFR at near normal level [17]. Furthermore, creatinine measurements collected from patients/family recall, were from different laboratories. However, renal function studies in large series of children undergoing

unilateral nephrectomy for oncological and not oncological indications show that mean GFR estimated with various traditional methods [2,11,12] reaches values quite similar to those found in the present study. In addition, in a previous article [12], data on GFR in relation to the age at the time of last investigation were presented graphically to facilitate a comparison with those of published reports. These article findings indicate that after unilateral nephrectomy 69% of patients with an age between 40 and 50 years, and 80% of patients with an age between 50 and 60 years presented a mild-to-moderate renal function loss [12]. These results parallel and validate present findings.

Another limitation of the present study is that our cohort includes a small number of children undergoing NSS. Furthermore, their relatively short follow-up do not necessary allow to conclude that NSS has a long-term benefit. However, the renal function advantage of NSS over nephrectomy has been documented in large series of adults so that for small renal cell carcinoma nephrectomy is not anymore regarded as the gold standard treatment [1]. Actually, the number of patients who developed decreased renal function is related more to the amount of renal parenchyma excised than to the histology of renal tumor.

An additional limitation of the present study is that nearly all patients had a mild renal function loss. Whether a mild renal function loss is associated or not with an increased risk of cardiovascular disease and overall mortality remains controversial. The most accepted view is that an eGFR between 60 and 89 ml/min/1.73 m^2, if not associated with albuminuria, should not be considered a chronic kidney disease [17]. However, a meta-analysis of adult population studies by using a novel method to summarize the published results, has come to the conclusion that an eGFR lower than 30% of that of subjects with two healthy kidneys (<90 ml/min/1.73 m^2), even in absence of kidney damage markers, is associated with a 20–30% increase in the risk of both major vascular events and of death from any cause at an age of 70 years [18].

An additional consideration is that we observed a significant decline in eGFR up to the fifth decade of life. As a 50-year-old patient can expect to live another three decades, it is reasonable to speculate that the great majority of patients undergoing nephrectomy during childhood for URT will experience a moderate-to-severe decrease of renal function. Strength of present study is the long period of post-operative follow-up. Our study suggests that children undergoing nephrectomy for URT may be at high risk to develop a mild-to-moderate renal function loss several decades after surgery.

In conclusion, the present study supports the concept that children undergoing nephrectomy for URT experience during the second decade of life a high prevalence (43%) of patients with mild renal function loss. In addition the study suggest that, in patients undergoing nephrectomy, the physiological age-related decline in renal function is probably responsible, during the fifth decade of life, for a significant increase in prevalence of patients with mild-to-moderate renal function loss. Therefore, the concept that renal function after unilateral nephrectomy is well preserved at long-term follow-up should be revised. Actually, adults undergoing nephrectomy during childhood for URT, like adults undergoing nephrectomy for renal cell carcinoma, often develop a decreased renal function that may increase their cardiovascular and overall mortality risk.

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