T Helper 17 Lymphocyte Pathway in the Diagnosis of Autosomal Dominant Polycystic Kidney Disease

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Introduction. Current assessment tools of autosomal dominant polycystic kidney disease (ADPKD) diagnosis are challenging. This study evaluated the possible application of assessment of interleukin (IL)-17-related cytokines and the circulatory T helper 17 cells in the diagnosis of ADPKD.

Materials and Methods. Enrolling 54 ADPKD patients and 54 healthy individuals, we measured serum and urine levels of IL-6, IL-17, IL-23, and transforming growth factor-β and the peripheral blood frequency of T helper 17 cells through flowcytometry. We computed sensitivity and specificity of each inflammatory marker as well as their different combinations using the receiver operating characteristic curve and discriminant function analysis.

Results. The mean serum and urine levels of IL-17 and IL-23 as well as urine levels of IL-6 were higher in ADPKD patients compared to the healthy controls ($P < .001$). There was no significant difference in the number of T helper 17 cells between the two groups. Among different combinations of the inflammatory markers, the serum IL-17 was the best factor in the diagnosis of ADPKD with a sensitivity as well as specificity of 100%.

Conclusions. It is likely that T helper 17 pathway is involved in the pathogenesis of ADPKD; therefore, it may be beneficial if such a pathway be considered in its diagnosis.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common progressive hereditary kidney disease that accounts for up to 10% of all patients with end-stage renal disease.[1,2] While cystogenesis is clearly linked to the *PKD1* or *PKD2* mutations,[1,3] the role of some humoral and cellular immune responses in such a phenomenon has just been demonstrated yet not distinctly been defined. A clear indication of such role is the inhibitory effects of some immunosuppressive drugs, such as glucocorticoids, mycophenolate mofetil, mammalian target of rapamycin, and tumor necrosis factor-α inhibitors, used as therapeutics in ADPKD patients.[4-6] Since there are many challenges accompanying current assessment tools of ADPKD diagnosis including both imaging and molecular approaches,[7,8] it seems that diagnostic biomarkers identifying different aspects of the disease such as kidney function impairment are of great importance.[9]

Interleukin (IL)-17, as the prototypic proinflammatory cytokine of T helper 17 (Th17) lymphocytes, has been associated with the pathogenesis of a range of autoimmune diseases including rheumatoid arthritis, systemic sclerosis, multiple sclerosis, and systemic lupus erythematosus[10-13]; therefore, it may be presumed

to be involved in ADPKD pathogenesis. Such involvement has been evaluated in some other kidney diseases such as glomerulonephritis, lupus nephritis, and immunoglobulin A nephropathy.[14-17] In this regard, cytokines which interplay some roles with IL-17 may have some potential role in pathogenesis as well as clinical status of ADPKD. T helper 17 cell lineage differentiation is driven by transforming growth factor-β (TGF-β) and IL-6, expanded and stabilized by IL-23.[18-25] Although many studies have focused on the IL-23-Th17 axis, the effect of IL-23 is evidenced in some diseases to be independent of IL-17 production.[26] Enhanced TGF-β in multiorgan autoimmune diseases can lead to dysregulated tissue repair, progressive fibrogenesis, and eventual end-organ damage,[27] and its highly expression in cyst epithelium of ADPKD patients is mostly correlated with the late stages of the disease.[28] An increased serum level of IL-6 has also been reported in even overt infection-free ADPKD patients whose proinflammatory system is highly activated and the anti-inflammatory defense system is weakened.[29]

To suggest the pathogenetic role of Th17 cells and the abovementioned cytokines, we compared the serum and urinary level of IL-17, IL-23, IL-6, TGF-β, and circulatory Th17 cells in a group of ADPKD patients to a control group. We hypothesized that these measurements may be a reflection of disease diagnosis in ADPKD patients.

MATERIALS AND METHODS

Participants

Fifty-four patients with ADPKD and 54 age-matched healthy individuals, all living in Kashan, an ADPKD-endemic city in the center of Iran, were enrolled in a case-control study. The diagnosis of ADPKD was confirmed by both a positive family history and the presence of 5 or more renal cysts on renal ultrasonography distributed to both kidneys. Demographic characteristics; renal manifestations including hematuria, proteinuria, urinary system infection, and urinary tract stones; extrarenal manifestations including hernias, liver and splenic cysts, and colonic diverticuli; and blood pressure were recorded on the data recruitment forms. None of the patients suffered from neither diabetes mellitus nor any other autoimmune or non-autoimmune inflammatory states and cancers, and none of them was on renal replacement therapy.

Blood and Urine Measurements

Serum and urinary levels of IL-17, IL-23, IL-6, and TGF-β, as well as the frequency of circulatory Th17 cells were measured. In addition, blood urea nitrogen, hemoglobin, and serum levels of low-density lipoprotein cholesterol, triglyceride, aspartate aminotransferase, alanine aminotransferase, and creatinine were measured in each group. Serum lipid levels were measured using end-point enzymatic methods according to Beckman Instruments, Fullerton, California's protocol. Creatinine level was assessed by a kinetic Jaffe method. Serum and urinary levels of selected cytokines were measured by a commercial sandwich type enzyme-linked immunosorbent assay kit (e-Bioscience, USA). The results were expressed as pg/mL. Blood and urine samples of all participants were taken exclusively after signing the informed consent form approved by the local ethics committee. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Flowcytometric Analysis

Suspensions of 2 million cells per milliliter in RPMI-1640 medium containing 10% fetal calf serum, 100 U/mL of penicillin, 100 mg/mL of streptomycin, and 2 mM glutamine (Invitrogen, Carlsbad, CA, USA) were prepared from peripheral blood mononuclear cells, which were isolated on standard Ficoll-Hypaque. The cells were stimulated by 50 ng/mL of phorbol myristate acetate and 1 μg/mL ionomycin for 5 hours in the presence of 1-mL Golgystop (BD-Bioscience, USA). After being washed once in phosphate-buffered saline, the cells were incubated in the dark at 4°C for 30 minutes to stain the surface with the anti-human CD4-FITC (eBioscience, USA). The cells were fixed, permeabilized (fixation-permeabilization buffer, eBioscience, USA), and incubated in the dark at 4°C for 30 minutes for intracellular staining with anti-human IL-17A-PE (BD-Bioscience, USA). Stained cells were analyzed by flowcytometric analysis using a BD FACS Calibur cytometer equipped with CellQuest software (BD Pharmingen, USA).

Statistical Analyses

The results were expressed as mean ± standard deviation. The groups were compared by the chi-square and independent *t* test. The Pearson coefficient was determined for correlating the

variables. Constructing discriminant functions, we determined diagnostic value of different models (containing different combinations of inflammatory markers) through canonical correlation and Wilk lambda assessment. We also determined the normal limit of each model. Using receiver operating characteristic curve and area under curve, we verified the sensitivity and specificity of each inflammatory marker as a diagnostic tool of ADPKD as well. The cutoff point for each marker was determined through Youden index. A *P* value less than .05 was considered significant. All analyses were made by the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Demographic, laboratory, and clinical characteristics of the patients and healthy controls are summarized in Tables 1 and 2. There were not any significant differences according to age, hemoglobin, serum low-density lipoprotein, serum IL-6, serum TGF-β, urine TGF-β, and circulatory Th17 cells. However, the APPKD group had a significantly frequency of men and higher values for serum creatinine, blood urea nitrogen, triglyceride, aspartate aminotransferase, and alanine aminotransferase;

Table 2. Clinical Characteristics of Patients With Autosomal Dominant Polycystic Disease

Clinical Characteristics	Value*
Renal manifestations	
Familial history	47 (87.0)
Duration of disease, mo	39.6 ± 9.0
Mean cyst size, mm	15.71 ± 2.1
Urinary calculi	43 (79.6)
Leukocyturia	25 (46.3)
Mild chronic kidney failure	54 (100)
Medications	
Angiotensin-converting enzyme inhibitors	38 (70.4)
Angiotensin receptor blockers	30 (55.6)
Diuretics	39 (72.2)
Antilipids	34 (63.0)
Allopurinol	4 (7.4)
Others	24 (44.4)
Accompanying diseases	
Liver cysts	26 (48.1)
Spleen cysts	26 (48.1)
Diverticulum	28 (51.9)
Peptic ulcer disease	12 (22.2)
Hypertension	9 (16.6)
Aneurysm	5 (9.3)
Diabetes	4 (7.4)
Gout	4 (7.4)
Fatty liver	1 (1.8)
Myelodisplastic syndrome	1 (1.8)
Urinary tract infection	1 (1.8)
None	15 (27.8)

*Values are percentages in parentheses.

Table 1. Baseline and Laboratory Characteristics of Patients With Autosomal Dominant Polycystic Disease (ADPKD) and Healthy Controls

Characteristic	ADPKD	Control	*P*
Number of participants	54	54	> .05
Sex			
Male	39	23	
Female	15	31	.002
Age, y	46.63 ± 15.88	44.63 ± 14.15	.49
Serum creatinine, mg/dL	1.56 ± 1.14	1.06 ± 0.21	.003
Blood urea nitrogen, mg/dL	23.42 ± 10.16	12.98 ± 4.42	< .001
Glomerular filtration rate, mL/min	61.76 ± 15.99	66.50 ± 3.30	.75
Hemoglobin, g/dL	13.94 ± 1.75	13.98 ± 1.45	.89
Systolic blood pressure, mm Hg	135.6 ± 17.2	112.8 ± 9.5	< .001
Diastolic blood pressure, mm Hg	90.9 ± 10.0	73.6 ± 9.5	< .001
Low-density lipoprotein, mg/dL	110.9 ± 38.1	104.7 ± 19.1	.28
Triglyceride, mg/dL	231.13 ± 94.63	80.24 ± 26.60	< .001
Alanine aminotransferase, U/L	39.37 ± 23.98	41.26 ± 11.70	.001
Aspartate aminotransferase, U/L	34.89 ± 20.10	22.61 ± 10.73	< .001
Serum interleukin-17, pg/mL	74.21 ± 19.77	13.68 ± 8.35	< .001
Urine interleukin -17, pg/mL	94.28 ± 49.30	9.14 ± 9.47	< .001
Serum interleukin -23, pg/mL	14.97 ± 5.40	5.70 ± 5.20	< .001
Urine interleukin -23, pg/mL	18.85 ± 11.80	4.61 ± 6.20	< .001
Serum interleukin -6, pg/mL	1.74 ± 0.92	1.59 ± 1.54	.54
Urine interleukin -6, pg/mL	2.77 ± 1.32	1.32 ± 1.35	< .001
Serum transforming growth factor-β, pg/mL	46.38 ± 15.03	40.57 ± 15.45	.05
Urine transforming growth factor -β, pg/mL	30.26 ± 9.72	28.96 ± 13.28	.56
T helper 17 cell count	1.42 ± 4.39	0.49 ± 0.49	.12

serum and urine levels of IL-17 and IL-23; and urine level of IL-6 than the healthy controls (Table 1).

Coefficiencies and goodness of fitting criteria of inflammatory markers in the diagnosis of ADPKD were evaluated in 8 combinational models of discriminant function as shown in Table 3. Model 1 explained 82.5% of variance of changes (r = 0.908). The general form of this model is as:

$Y = -2.717 + 0.079 \times \text{serum IL-17} - 0.001 \times \text{urine IL-17} - 1.057 \times \text{Th17}$

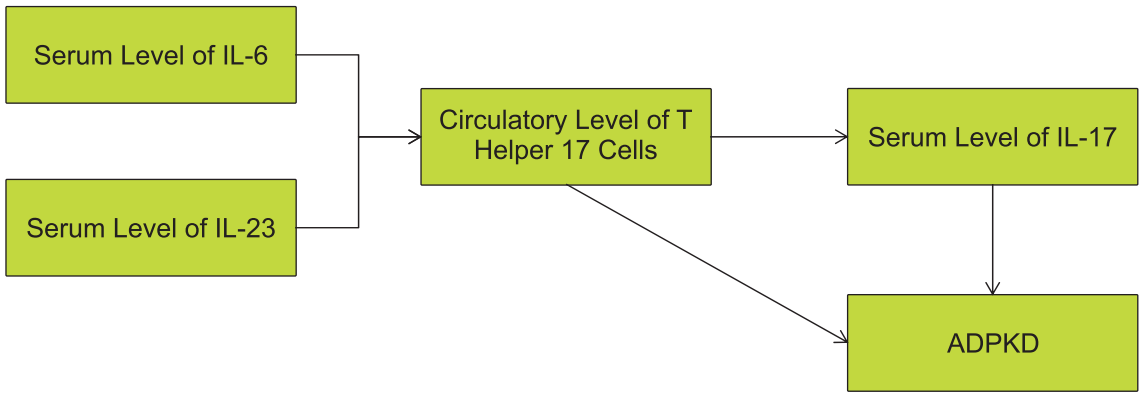
Having considered little value of urine IL-17 coefficient in the model, we omitted that in model 2 whose canonical correlation coefficient decreased to such a little value of 0.9. In model 3, canonical correlation coefficient reached 0.698, which could not explain 51.2% of variance; therefore, inflammatory markers could weakly fit in the diagnosis of ADPKD in such model. There was the most canonical correlation coefficient (r = 0.921) in model 4, which could not explain only 15.2% of changes. There was a canonical correlation coefficient of 0.79 in model 5, which

Table 3. Coefficiencies and Goodness of Fitting Criteria of Inflammatory Markers in the Diagnosis of Autosomal Dominant Polycystic Disease According to Discriminant Function Model

Model	Coefficient	Canonical Correlation	Wilk Lambda	Normal Limit
Model 1		0.908	0.175	-2.173, 2.133
Serum interleukin-17	0.079			
Urine interleukin-17	-0.001			
T helper 17	-1.057			
Constant	-2.717			
Model 2		0.9	0.191	-2.042, 2.042
Serum interleukin-17	0.066			
T helper 17	0.070			
Constant	-2.984			
Model 3		0.698	0.512	-0.967, 0.967
Serum interleukin-23	0.130			
Urine interleukin-23	0.051			
Constant	-1.945			
Model 4		0.921	0.152	-2.343, 2.343
Serum interleukin-17	0.084			
Serum interleukin-23	-0.035			
Serum interleukin-6	-0.443			
Constant	-2.584			
Model 5		0.79	0.376	-1.289, 1.265
Urine interleukin-17	0.023			
Urine interleukin-23	0.035			
Urine interleukin-6	0.090			
Constant	-1.777			
Model 6		0.916	0.161	-2.279, 2.237
Serum interleukin-17	0.097			
Urine interleukin-17	-0.003			
Serum interleukin-23	-0.063			
Urine interleukin-23	-0.001			
Urine interleukin-6	-0.155			
T helper 17	-0.843			
Constant	-2.587			
Model 7		0.916	0.162	-2.256, 2.256
Serum interleukin-17	0.092			
Serum interleukin-23	-0.06			
Urine interleukin-6	-0.142			
T helper 17	-0.893			
Constant	-2.546			
Model 8		0.896	0.198	-1.994, 1.994
Serum interleukin-17	0.066			
Constant	-2.895			

was manifested as a weak model in diagnosis of ADPKD. Comparing models 4 and 5, we could show a better diagnostic accuracy through serum (and not urine) sampling. In model 6, we considered all serum and urine markers and reached a more accurate canonical correlation coefficient of 0.916 (full model), but it showed a weak effect from urine IL-17 as well as IL-23. Having omitted these 2 markers in model 7, we did not obtain a lower goodness of fitting. We also reached a proper canonical correlation in model 8, which only contains the measurement of serum level of IL-17. Among different markers, only serum level of IL-17 could explain a variance of 96.4% (r = 0.896), which was just 4.6% less than that in model 4. Taking all models together, functional analysis proposed a model (Figure) which introduces both number of circulatory Th17 cells and serum level of IL-17 as proper diagnostic tools of ADPKD.

According to Table 4, which shows observed and



A proposed model to introduce both number of circulatory T helper 17 cells and serum level of interleukin (IL)-17 as diagnostic tools of autosomal dominant polycystic disease (ADPKD)

Table 4. Observed and Predicted Frequencies and Diagnostic Criteria of Inflammatory Markers in the Diagnosis of Autosomal Dominant Polycystic Disease According to Discriminant Function Model*

Observed	Predicted		Diagnostic Test				
	Negative	Positive	Sensitivity	Specificity	PPV	NPV	Corrected Classification
Model 1			100	98.1	98.2	100	99.1
Control	53	1					
Case	0	54					
Model 2			98.2	100	100	98.2	99.1
Control	54	0					
Case	1	53					
Model 3			83.3	79.6	80.4	82.7	81.5
Control	43	11					
Case	9	45					
Model 4			100	100	100	100	100
Control	54	0					
Case	0	54					
Model 5			81.5	98.1	97.8	84.1	89.8
Control	53	1					
Case	10	44					
Model 6			100	98.1	98.2	100	99.1
Control	53	1					
Case	0	54					
Model 7			100	100	100	100	100
Control	54	0					
Case	0	54					
Model 8			96.3	100	100	96.4	98.1
Control	54	0					
Case	2	52					

*PPV indicates positive predictive value and NPV, negative predictive value.

predicted frequencies of inflammatory markers in the diagnosis of ADPKD, except for models 3 and 5, other models showed a high accurate diagnostic value in ADPKD. Considering validity criteria in all models, we concluded that model 4, which was the best among combinational models, had a corrected classification of 100%. It means that all patients would not miss the ADPKD diagnosis via measurement of the markers included in that model. Diagnostic values in model 8 reached 98.1%, which was just 1.9% less than that in model 4.

Using receiver operating characteristic analysis and computing area under the curve, we tried to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and corrected classification of each inflammatory marker as a diagnostic tool of ADPKD (Table 5). The sensitivity and specificity of 100% as well as the area under the curve of 1 was found for the serum level of IL-17 with the cutoff point of 35.3.

To evaluate the correlation between the inflammatory markers and chronic kidney failure (CKF), we divided all patients with or without CKF according to glomerular filtration rate. As shown in Table 6, except for serum level of TGF-β (P = .03), there was not a significant difference between the patients with and without CKF according to different inflammatory markers. Among different markers, serum and urine levels of TGF-β had positive correlations with the glomerular filtration rate.

DISCUSSION

In line with the documented role of inflammation in ADPKD,[30] emphasis has continuously been done on the pathogenic effects of increased levels of some inflammatory factors including cyst levels of IL-1β, IL-2, tumor necrosis factor-α, stromelysinin, and serum levels of IL-6, IL-8, ICAM-1, VCAM-1, and MCP-1.[5,28,31] The T helper17 pathway components including IL-23, Th17 cells, and IL-17 have been introduced to be evolved in chronic inflammation of some tissue-specific autoimmune disorders,[10-13] as well as kidney diseases,[14-17] suggesting the potential role of IL-23-Th17 axis on renal tissue inflammation. Considering ADPKD as a local rather than systemic disorder, we showed, for the first time, the increased serum and urinary inflammatory markers of IL-17 and IL-23 in a group of ADPKD patients. Such a concept could be confirmed considering that anti-

Table 5. Validity Indexes of Each Inflammatory Marker for Autosomal Dominant Polycystic Disease Diagnosis*

Factors	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Corrected Classification	Yuden Index
Serum interleukin-17	35.3	1	100	100	100	100	100	1
Urine interleukin-17	27.05	0.994	98.1	96.2	96.4	98.1	97.2	0.943
Serum interleukin-23	9.25	0.887	88.9	79.6	81.4	87.8	84.3	0.685
Urine interleukin-23	11.5	0.899	88.9	85.2	85.7	88.5	87	0.741
Serum interleukin-6	1.275	0.618	70.4	57.4	60.3	64.4	62	0.278
Urine interleukin-6	1.175	0.83	90.7	68.5	69	86.5	75	0.592
T helper 17	0.615	0.771	81.5	72.2	74.6	79.6	76.9	0.537

*PPV indicates positive predictive value; NPV, negative predictive value; and AUC, area under the curve.

Table 6. Mean Values of Inflammatory Markers According to Chronic Kidney Failure and Linear Correlation Coefficients Between These Markers and Glomerular Filtration Rate*

	CKF			Correlation With GFR	
Inflammatory Markers	GFR > 60 mL/min	GFR ≤ 60 mL/min	*P*	Coefficient	*P*
Serum interleukin-17	71.9 ± 18.9	76.5 ± 20.7	.40	-0.286	.04
Urine interleukin-17	82.9 ± 51.2	105.7 ± 45.4	.09	-0.314	.02
Serum interleukin-23	13.7 ± 3.9	16.2 ± 6.4	.09	-0.233	.09
Urine interleukin-23	18.0 ± 7.0	19.7 ± 15.3	.61	-0.095	.49
Serum interleukin-6	1.61 ± 0.92	1.89 ± 0.93	.27	-0.195	.16
Urine interleukin-6	2.64 ± 1.37	2.92 ± 1.28	.44	-0.059	.67
Serum TGF-β	50.7 ± 13.2	42.0 ± 15.8	.03	0.341	.01
Urine TGF-β	32.2 ± 9.4	28.3 ± 9.8	.14	0.171	.22
T helper 17	0.79 ± 0.26	0.86 ± 0.42	.46	-0.226	.10

*CKF indicates chronic kidney failure; GFR, glomerular filtration rate; and TGF, transforming growth factor.

IL-17-IL-23 axis therapies show promising results in some human clinical trials such as those related to psoriasis.[25] We demonstrated that urinary (but not serum) levels of IL-6 were significantly higher in our ADPKD patients than those in the control group; therefore, there is a more local secretion of this serum acute phase protein instead of its systemic secretion. However, there was no significant difference in serum and urinary levels of TGF-β between our two groups. This finding might be due to TGF-β suppressing agents prescribed for our patients, ie, angiotensin-converting enzyme inhibitors, methylprednisolone, and rosiglitazone.[32-34] Furthermore, TGF-β signaling is strongly increased at more advanced stages of ADPKD,[35] and our patient population comprised a typical group in terms of organ involvement, degree and duration of the disease, and the kind of prescribed immunosuppression regimen.

Evaluating the correlation between different markers and CKF, we did not find a significant difference between the CKF and different markers except for the serum level of TGF-β. This may be due to a mild CKF among CKF-positive patients and could be confirmed by partially high correlation coefficient of each marker with glomerular filtration rate. Since serum and urinary levels of anti-inflammatory marker of TGF-β showed positive correlations with glomerular filtration rate, it seems that, among different markers, such marker may improve the kidney function of the patients.

Since there are many challenges accompanying current assessment tools of ADPKD diagnosis,[7-8,36] we designed different models containing different combinations of serum and urinary levels of the mentioned inflammatory markers in the diagnosis of ADPKD. Having compared different models, we found a better diagnostic accuracy through serum (but not urine) sampling. We also showed that the combination of serum levels of IL-17, IL-23, and IL-6 showed the best criterion in the diagnosis of ADPKD, especially considering this that such combination lacks evaluating the number of Th17 cells whose measurement is expensive and is not available in most routine laboratories. To introduce just one marker as the diagnosis of ADPKD, we determined the measurement of serum level of IL-17 as the best option while taking into account the simplicity of its measurement, cost-effectiveness, and no necessity to any other calculation regarding the combination with other markers. Additionally, such measurement shows the sensitivity and specificity of 100% with the cutoff point of 35.3.

Our study enjoyed a relatively proper sample size and associated standard deviations that yield a proper power to detect differences in analysis of the groups. There were no essential factors affecting the inflammatory status of the patients including any other autoimmune and non-autoimmune inflammatory states and cancers. We considered such a proper integrity of counteracting factors related to Th17 subset. The limitation of our study was that first, we did not monitor the changes of selected cytokines longitudinally. This limitation allowed just a cross-sectional analysis of cytokine profiles of only limited robustness. Second, functional assays, which provide further information on the immuno-effectory status of the patients, were not performed. Such study may provide deeper insights into the functional role of Th17 pathway in the control of ADPKD.

CONCLUSIONS

Our study suggests that Th17 cells and related cytokines may take part in ADPKD pathogenesis through their potent pro inflammatory capacity. An array of these factors may be considered as useful diagnostic markers of ADPKD patients.

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CONFLICT OF INTERETST

None declared.

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